THE CHEMISTRY OF NATURAL PRODUCTS
VOLUME VII

K. W. BENTLEY

THE ALKALOIDS
Part II

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Alkaloids: Part-..

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K. W. BENTLEY, ***Editor***

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THE CHEMISTRY OF NATURAL PRODUCTS

A series of texts on the constitution of natural products

K. W. BENTLEY, *Editor*

VOLUME VII

THE ALKALOIDS

Part II

K. W. BENTLEY

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Alkaloids: Part-..

PREFACE

In reviewing Part I of this series, E. Wenkert criticized it on the grounds that several important groups of alkaloids had been omitted. These omissions were intentional, since it seemed to the author that in most cases the groups had been insufficiently explored. The time now seems opportune, however, to remedy this fault by the publication of a second volume devoted to those groups of alkaloids not dealt with in Part I.

Kingston-upon-Hull, England K. W. B.
January 1964

To

DAVID GRAEME BENTLEY

the most active of natural products

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CHAPTER 1

ALKALOIDS OF THE IMIDAZOLE GROUP

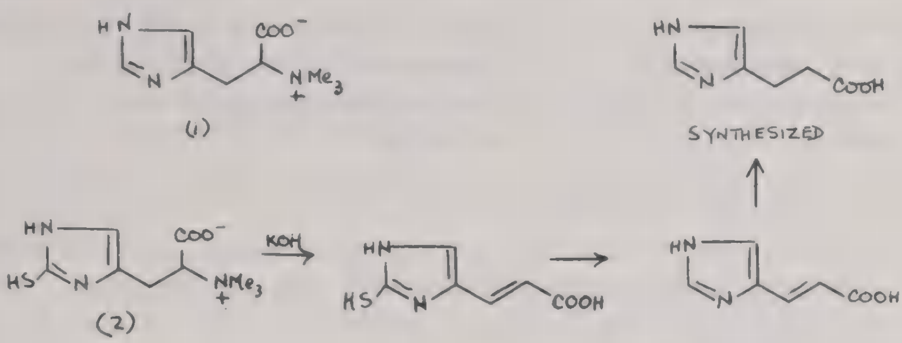
There are only a few representatives of the imidazoles among the naturally occurring vegetable bases. Histamine has been isolated from ergot and a dimethylhistamine from *Geodia gigas*. Hercymine is a derivative of histidine having the structure (1)[10, 11] and ergothioneine, also from ergot, is the corresponding thiol (2).[2, 5] The structure of the last of these bases was demonstrated by the degradations and synthesis set out on page 3.

Pilocarpine, Isopilocarpine

These two diastereoisomeric bases are found in various *Pilocarpus* species, especially *P. jaborandi*. Pilocarpine may be converted into isopilocarpine under a variety of conditions, such as heating alone or as the hydrochloride at 200°, or with aqueous sodium hydroxide or alcoholic sodium ethoxide.[13] The reverse change may be accomplished only to a limited extent.[8]

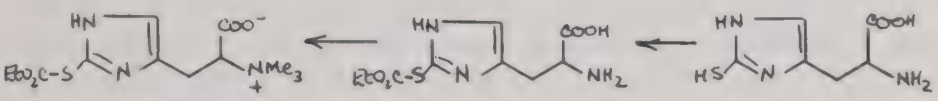
The two bases have the composition $C_{11}H_{16}O_2N_2$ and are monoacid bases containing one —NMe— group but no reducible double bonds. That they contain a lactone system, which accounts for both oxygen atoms, is demonstrated by their conversion into pilocarpic and isopilocarpic acid by alkalis, from which the original bases may be regenerated.[13] Isopilocarpic acid has been shown to have the composition $C_{11}H_{18}O_3N_2$, i.e. $C_{11}H_{16}O_2N_2 + H_2O$.[14] Ethyl γ-chloropilocarpate and the corresponding isomer are obtained by treatment of the bases with ethanolic hydrogen chloride.[15]

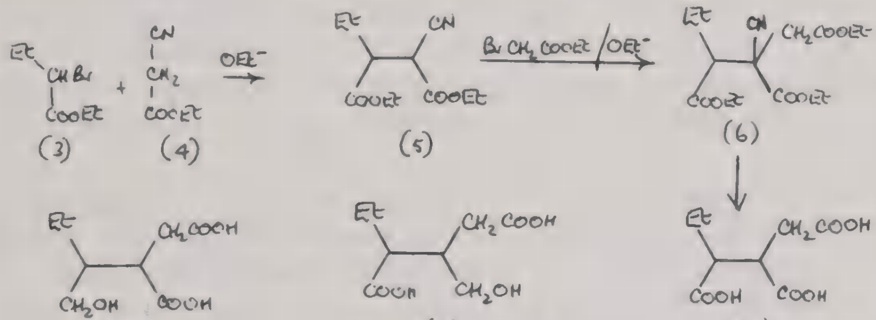
Oxidation with alkaline permanganate results in the formation of a mixture of homoisopilopic and isopilopic acids from both bases. The latter, $C_7H_{10}O_4$, is a monobasic acid that still contains the lactone system, as can be demonstrated by the formation of a hydroxydiamide; it is converted into n-butyric acid on alkali fusion. Homoisopilopic acid, $C_8H_{12}O_4$, which is likewise a lactonic acid, on alkali fusion is transformed into (+)-α-ethyltricarballylic acid, $C_8H_{12}O_6$ (7), synthesized by the route (3) → (7). This change occurs without loss of carbon and can only be attributed to oxidation of CH_2OH (from opening of the lactone ring) to COOH, leading to three possible structures (8), (9) and (10) for the hydroxy acid corresponding to homoisopilopic acid. As the



(1)

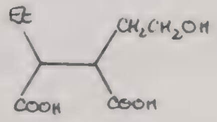
(2)





(3) (4) (5) (6)

(9) (8) (7)

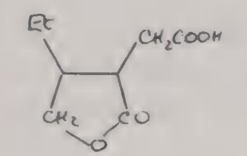


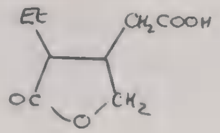
(10)

last named acid is, from its stability to cold alkali, clearly a γ-lactone, four possibilities for its structure arise, namely (11) → (14). Since isopilopic acid is clearly a further oxidation product of homoisopilopic acid and must arise from the oxidation of $—CH_2COOH$ to $—COOH$, structures (13) and (14) can be discounted. The two structures for isopilopic acid corresponding to (11) and (12) for its homologue are (15) and (16), of which (15) is a derivative of malonic acid and would be expected to lose carbon dioxide readily, and since isopilopic acid is stable at 200° it must be assigned the structure (16), and homoisopilopic acid must be (12).[6, 7]

Distillation of isopilocarpine with soda-lime results in the production of ammonia, methylamine, 1-methylimidazole (17), 1,5-dimethylimidazole (18) and 5-n-amyl-1-methylimidazole (19).[7] The structure of (18) was demonstrated by degradation to (±)-*N*-methylalanine (21) as shown,[24] and by synthesis from α-methylaminopropionaldehyde diethylacetal (22) via (23) and (24).[3] 5-n-Amyl-1-methylimodazole (19) has been synthesized by a similar route and shown to be identical with the product of degradation of isopilocarpine,[1] which must therefore be (25).[14]

This structure has been confirmed by the ozonolysis of isopilocarpine which affords homoisopilopic acid methylamide (26), ammonia, formic acid and carbon dioxide. The ozonolysis of pilocarpine, however, affords the methylamide of homopilopic acid, which must be a diastereoisomer of homoisopilopic acid and thus pilocarpine and isopilocarpine must be diastereoisomers, the seat of isomerism doubtless being the hydrogen-bearing carbon atom α to the carbonyl group.[12] These ozonolyses finally eliminate the possibility that pilocarpine and isopilocarpine are positional isomers of a substituted imidazole.


(11)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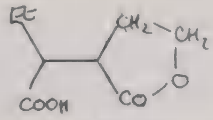
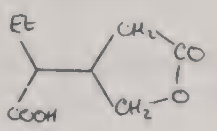
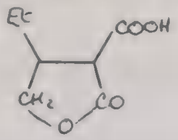
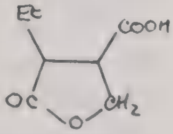
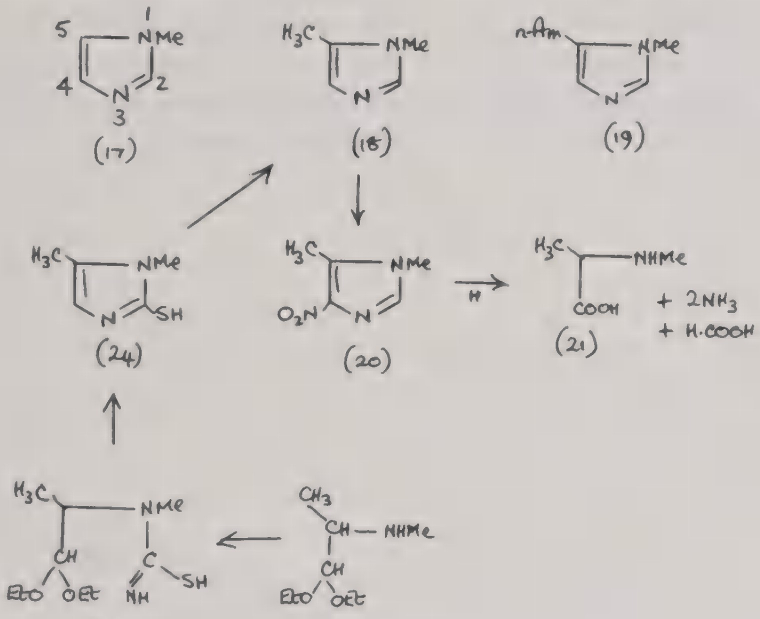

(13)

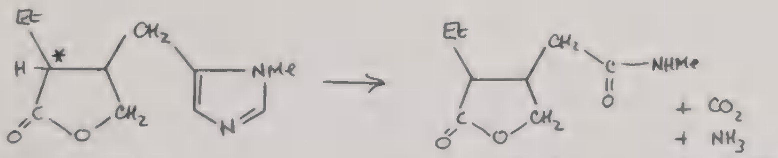

(14)


(15)


(16)



(17) (18) (19) (24) (20) (21) (23) (22)



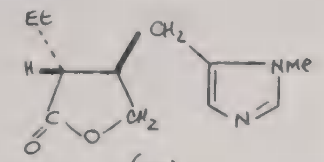
(25) (26)

It seems very probable that isopilocarpine, which is heavily favoured at equilibrium, has the ethyl and imidazolylmethyl groups disposed in the *trans* relationship on the lactone ring (27) and pilocarpine has these groups *cis* (28).

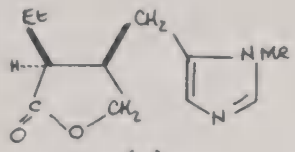
The gross structure (25) has been confirmed by the synthesis of both pilocarpine and isopilocarpine in stages as follows:

1. The synthesis of pilopic and isopilopic acids as shown in (29) → (32a and b).[16, 18, 25]
2. The conversion of isopilopic acid into homoisopilopic acid by the route (32b) → (33b)[17] and of pilopic acid (32a) into homopilopic acid (33a) by the Arndt–Eistert process.[19]
3. The synthesis from these two acids (33) of isopilocarpine and pilocarpine respectively as outlined in (33) → (40).[9, 21, 22] An alternative synthesis, (41) → (50), of both bases has been achieved.

In this the intermediate acid (43) was separated into two diastereoisomeric racemates and these furnished homoisopilopic and homopilopic acids (44), leading eventually to the two alkaloids.[4]



(27)



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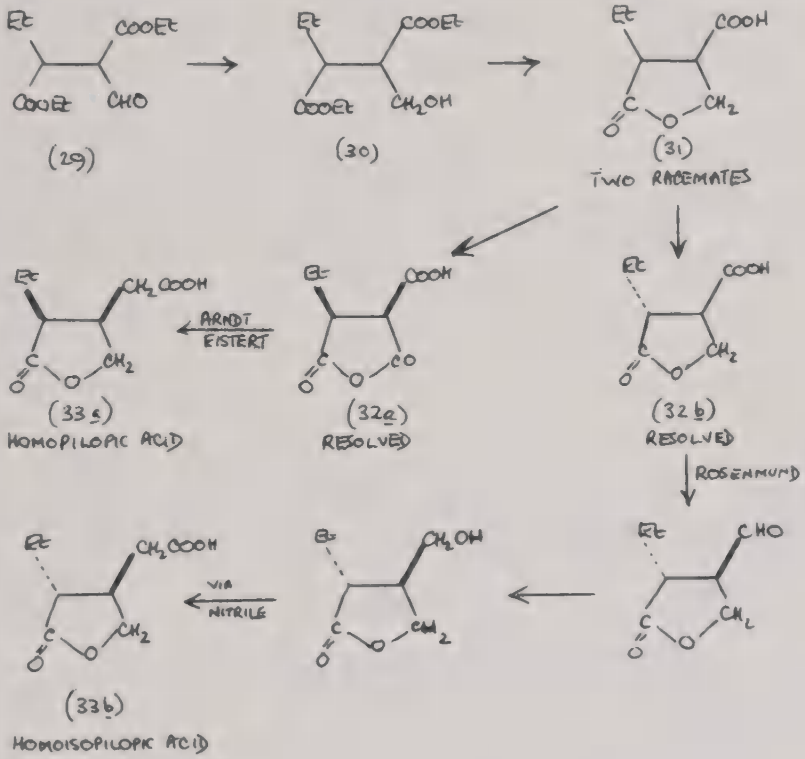
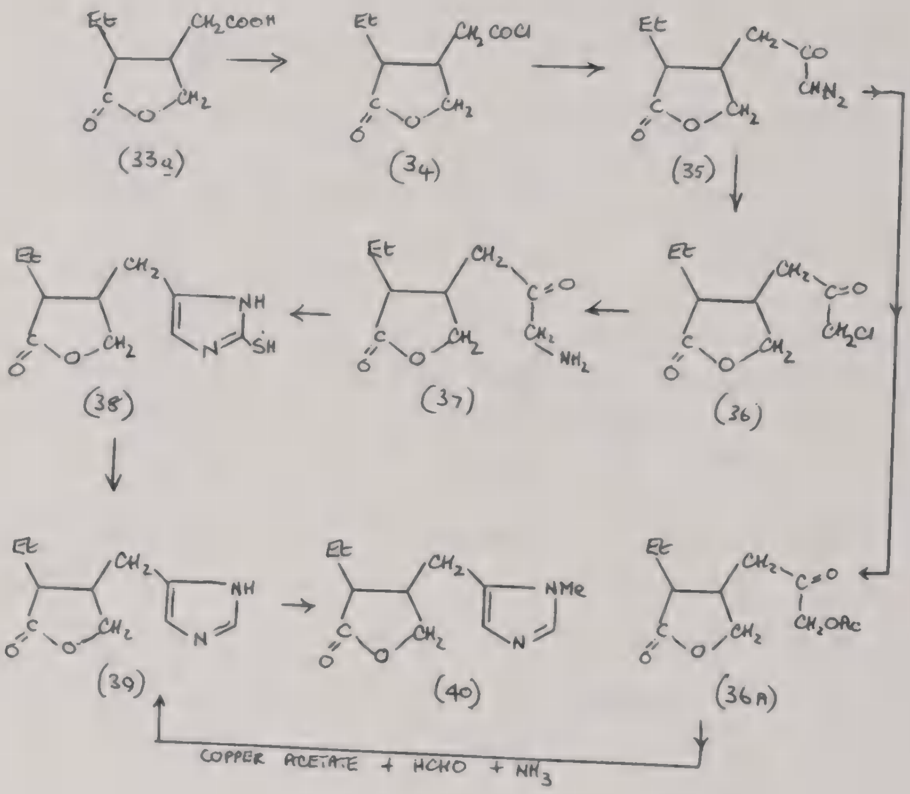
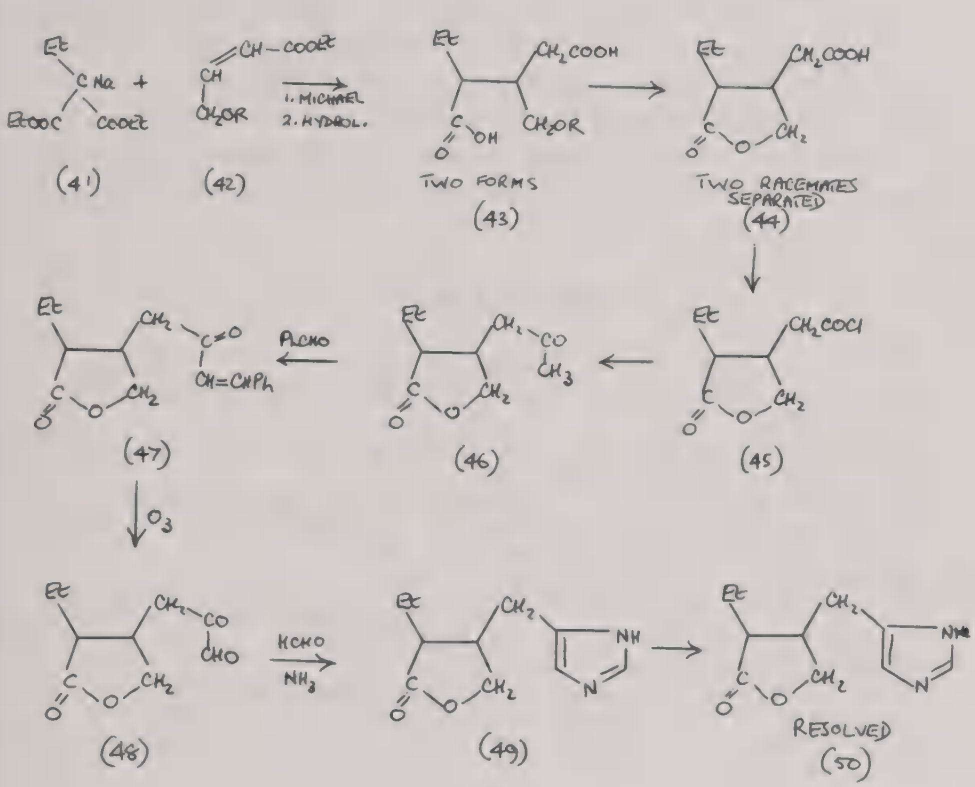

(29)
(30)
(31)
TWO RACEMATES
(32a)
RESOLVED
(32b)
RESOLVED
ROSENMUND
ARNDT EISTERT
(33a)
HOMOPILOPIC ACID
VIA NITRILE
(33b)
HOMOISOPILOPIC ACID


(33a)
(34)
(35)
(36)
(37)
(38)
(39)
(40)
(36A)
COPPER ACETATE + HCHO + NH3


1. MICHAEL
2. HYDROL.
(41)
(42)
TWO FORMS
(43)
TWO RACEMATES SEPARATED
(44)
(45)
(46)
PhCHO
(47)
O3
(48)
HCHO
NH3
(49)
RESOLVED
(50)

Pilosine

This is a minor alkaloid from *Pilocarpus microphyllus*. It has the composition $C_{16}H_{18}O_3N_2$, and is a monoacid base containing one —NMe— group. Like pilocarpine it can be shown by titration with hot alkali to contain a lactone ring. With boiling 20% aqueous potassium hydroxide it is degraded to benzaldehyde and pilosinine $C_9H_{12}O_2N_2$. On the assumption that this reaction represents a dealdolization, pilosine is assigned the constitution (51), pilosinine (52) and anhydropilosine, which is readily obtained by the dehydration of the alkaloid, the structure (53).[23] These are supported by a synthesis of pilosinine shown in (54) → (59) → (52).[20]

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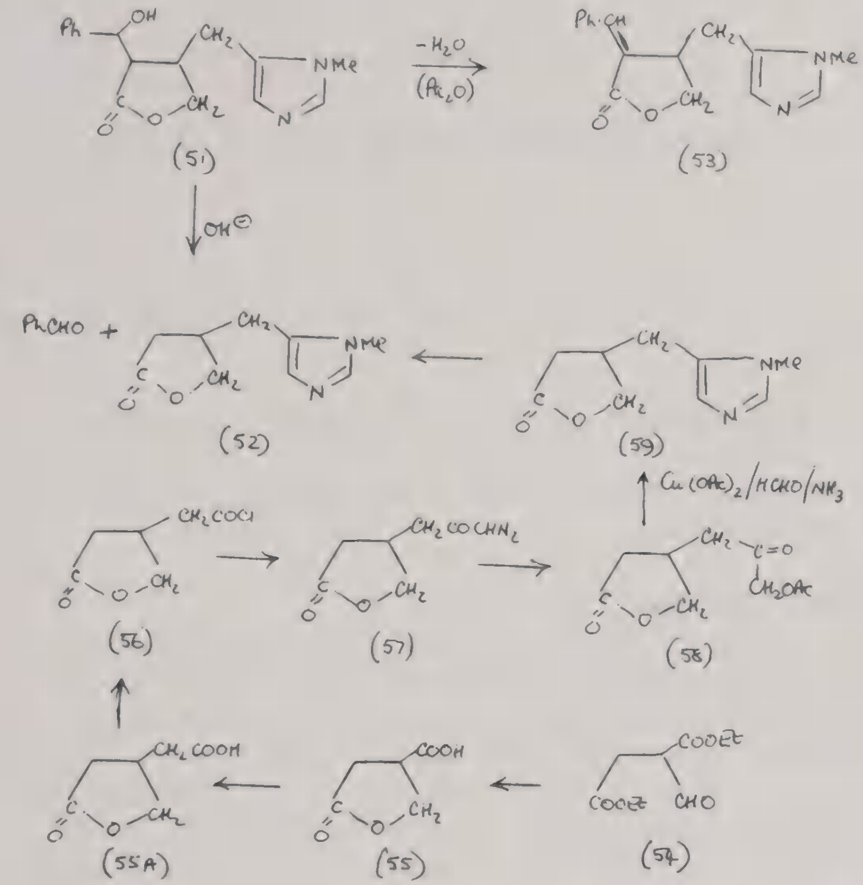

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CHAPTER 2

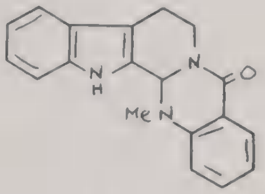
THE QUINAZOLINE ALKALOIDS

Only a few alkaloids are known derived from quinazoline and of these evodiamine (1) and rutaecarpine (2), containing an indole system, are discussed in Chapter 8. Vasicine and febrifugine and isofebrifugine are considered here.

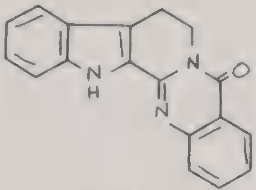
Vasicine (Peganine) (22)

This is obtained from the leaves of the Indian plant *Adhatoda vasica* Nees and from the seeds of *Peganum harmala* L. (which also contains the indole alkaloid harmine), and has the composition $C_{11}H_{12}ON_2$. It is a monoacidic tertiary base containing no —NMe— group, one active hydrogen atom and one acetylatable non-phenolic hydroxyl group.[13] This hydroxyl group may be replaced by chlorine by the action of phosphorus oxychloride, and the product on reduction yields deoxyvasicine.[11]

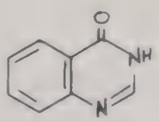
As the alkaloid can be oxidized to 4-quinazolone (3) and as potash fusion of the base yields anthranilic acid (4), it was first assigned the structure of 2-propyl-4-quinazolone, but neither the n-propyl nor the i-propyl compounds of this constitution were found on synthesis to be identical with the alkaloid.[5] Oxidation of the base under less vigorous conditions, however, led to an acid $C_{10}H_8O_3N_2$ which was shown to have the structure (5) by decarboxylation to 3-methyl-4-quinazolone and hydrolysis to anthranilic acid (4)[13] and glycine, and by synthesis as shown in (6) → (7) → (5) of the methyl ester.[10] These results led to the proposal of structure (8) for vasicine, but the base shows none of the properties of a carbinolamine and material of this structure prepared by synthesis was not identical with the alkaloid.[9]


NH
N
O
Me N

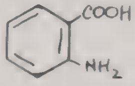
(1)


NH
N
O
N

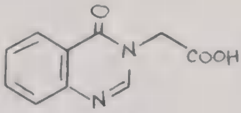
(2)


O
NH
N

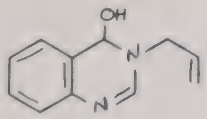
(3)


COOH
NH2

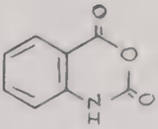
(4)


O
N
COOH
N

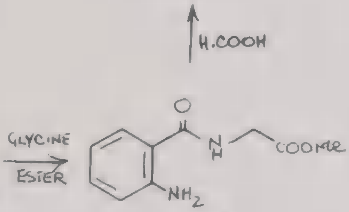
(5)


OH
N
N

(8)


O
O
O
NH

(6)

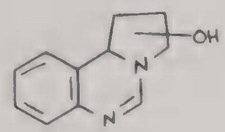

H.COOH
GLYCINE
ESTER
O
NH
COOMe
NH2

(7)

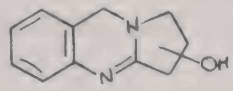
As vasicine is resistant to hydrogenation it must be tricyclic and of the two possible arrangements (9) and (10) the latter was preferred since deoxyvasicine like 2-alkyl-4-quinazolones, 2-alkylpyridines, etc., readily condensed with benzaldehyde to give the styrene derivative (11) indicating that this base contains a reactive methylene group.[6, 7]

The structure (12) for deoxyvasicine was then confirmed by two independent syntheses (13) → (14) → (12)[11] and (15) → (17) → (12),[6] thus settling the nature of the basic ring system.

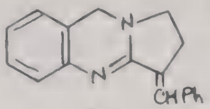
The position of the hydroxyl group in vasicine was demonstrated by the synthesis of the alkaloid as shown in formulae (18) → (22)[12] and (23) → (22).[14]


OH
N
N

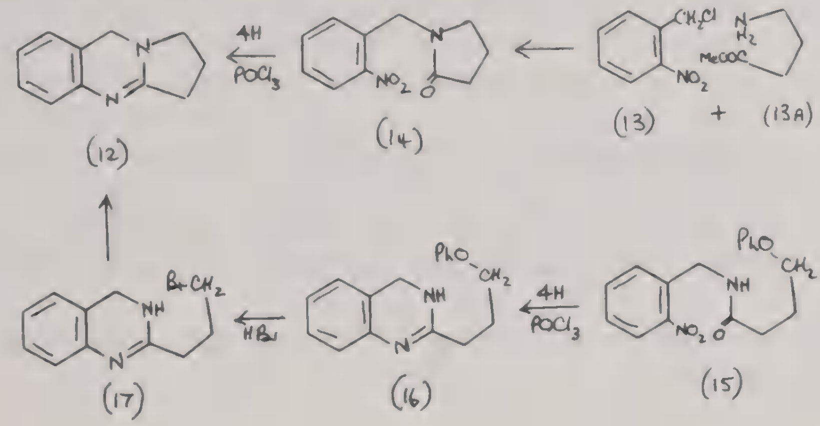
(9)

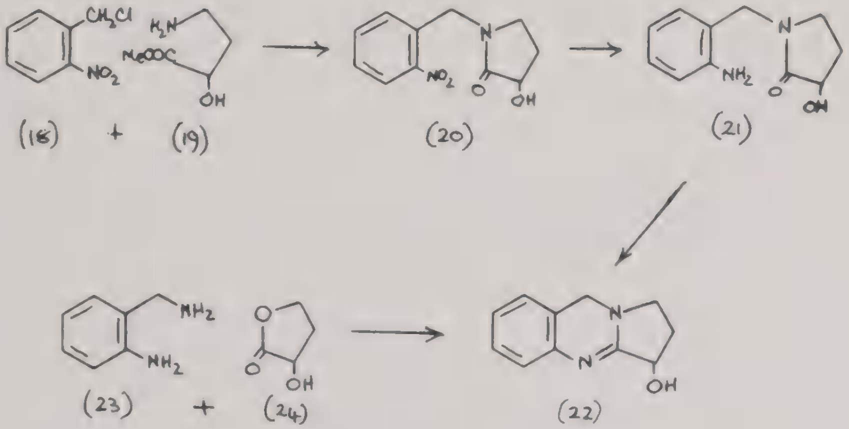

N
N
OH

(10)


N
N
CHPh

(11)


(12)
4H
POCl$_3$
(14)
CH$_2$Cl
NH$_2$
MeOOC
NO$_2$
(13) + (13A)
(17)
BrCH$_2$
HBr
(16)
PhO
CH$_2$
4H
POCl$_3$
(15)

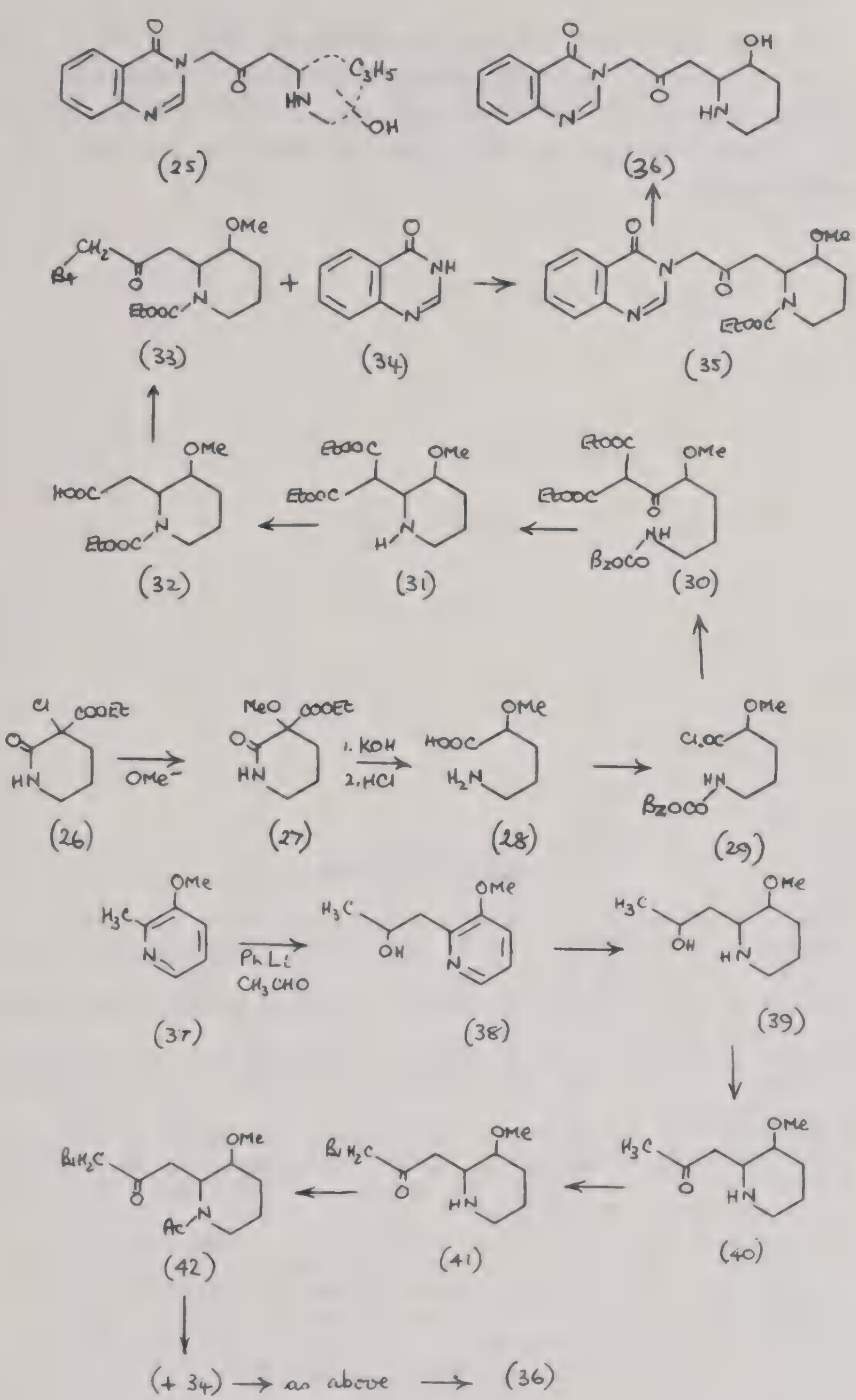

CH$_2$Cl
H$_2$N
MeOOC
NO$_2$
OH
(18) + (19)
(20)
NH$_2$
(21)
NH$_2$
NH$_2$
(23) + (24)
(22)

Febrifugine and Isofebrifugine

These two isomeric bases from *Dichroa febrifuga* have the composition $C_{16}H_{19}O_3N_3$. They contain neither —COOH, —OMe, —O—CH_2—O— nor —NMe— groups. Febrifugine contains a carbonyl group and an —NH— group since it readily gives an oxime and an *N*-nitroso derivative, and an acetylatable hydroxyl group.

With alkaline permanganate both alkaloids give 4-quinazolone[4] whereas neutral permanganate yields 4-quinazolone-3-acetic acid (5) already obtained from vasicine.[8] The secondary amino group was thought to be β to the carbonyl group since cyclic products were obtained with phenylisothiocyanate and with potassium cyanate. The *O*-acetyl ester is deacetylated during formation of an oxime suggesting spatial proximity of the carbonyl and hydroxyl groups. These findings led to the part structure (25) and total synthesis of a number of possible structures soon demonstrated that febrifugine has the structure (36).[3]

The first synthesis was achieved by the route (26) → (36),[3] but the simplest process is as shown in (37) → (42) → (36).[1]


(25)
(36)
(33)
(34)
(35)
(32)
(31)
(30)
(26)
OMe⁻
(27)
1. KOH
2. HCl
(28)
(29)
(37)
PhLi
CH_3CHO
(38)
(39)
(40)
(41)
(42)
(+ 34) → as above → (36)

Isofebrifugine is very probably the hemiketal (43); its IR spectrum shows no carbonyl absorption, whereas febrifugine shows an IR absorption band at 1727 cm^{-1}; the hydrogen bonding between hydroxyl and carbonyl groups in (43) could account for the stability of isofebrifugine.[2]

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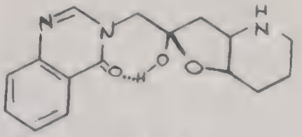
13. Späth, E., and E. Nikawitz, *Ber.*, **67**, 45 (1934).
14. Späth, E., and N. Platzer, *Ber.*, **69**, 255 (1936).



(43)

CHAPTER 3

THE PYRROLIZIDINE ALKALOIDS

The bases of this group, generally referred to as the Senecio alkaloids, occur naturally in various *Senecio*, *Crotalaria* and *Heliotropium* species; they are very toxic, causing liver necrosis and death, especially in animals eating fodder contaminated with alkaloid-bearing plants, among which are quite common weeds such as ragwort. They are all alkamine esters and readily undergo hydrolysis to give an alkanolamine (termed a *necine*) and an acid or acids (*necic acid*). An alternative mode of fission of the molecule is also available in a number of cases in which the alkanolamine is an allylic alcohol; these bases may be subjected to hydrogenolysis, when the products are a necic acid as before or, in certain cases, a reduced necic acid, and a modified necine that has lost a hydroxyl group and may also have suffered reduction.

The necines and necic acids are conveniently considered separately.

THE NECINES

Five groups of necine of known structure may be identified: $C_8H_{15}NO$, the related unsaturated $C_8H_{13}NO$, $C_8H_{15}NO_2$, the corresponding unsaturated $C_8H_{13}NO_2$, and $C_8H_{15}NO_3$. Retronecine-*N*-oxide has the composition $C_8H_{13}NO_3$ but is correctly regarded as a derivative of $C_8H_{13}NO_2$; other necine-*N*-oxides also occur naturally as their necic acid esters.

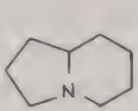
Retronecine and Heliotridine

These two necines, the products of hydrolysis of the alkaloids retrorsine and heliotrine respectively, as well as of several others, are diastereoisomers of composition $C_8H_{13}NO_2$. They contain two hydroxyl groups one of which is more easily esterified than the other and this OH group is removed by hydrogenolysis over platinum oxide, when a double bond is also saturated, four atoms of hydrogen being absorbed. The products of hydrogenolysis are retronecanol and oxyheliotridane, which are also the respective products of hydrogenolysis of the parent alkaloids retrorsine[18] and heliotrine.[41] Dehydration of retronecanol and oxyheliotridane afford unsaturated bases of composition $C_8H_{13}N$ that on reduction give the same saturated base, heliotridane $C_8H_{15}N$. The same base may also be obtained in stages as shown from platynecine $C_8H_{15}NO_2$,[34] the product of hydrolysis of the alkaloid platyphylline; *platynecine* is obtainable by the hydrogenation over nickel (which does not involve hydrogenolysis) of retronecine,[11] and is therefore dihydroretronecine.

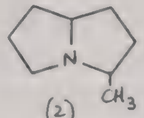
$$\begin{tikzcd}
\text{Heliotridine} \arrow[r, "H_2/PtO_2"] & \text{oxyheliotridane} \arrow[r, "-H_2O"] & C_8H_{13}N \arrow[dr] & \\
\text{Retronecine} \arrow[r, "H_2/PtO_2"] \arrow[d, "H_2Ni"] & \text{retronecanol} \arrow[r] & C_8H_{13}N \arrow[r, "H_2Pt"] & \text{HELIOTRIDANE} \\
\text{Platynecine} \arrow[r] & \text{dichloroplatynecine} \arrow[urr, "Na/EtOH"] & &
\end{tikzcd}$$

The composition of the saturated heliotridane indicates the presence in the molecule of two rings, and the retention of the nitrogen atom after two Hofmann degradations shows that this atom is common to both rings. One such Hofmann degradation followed by reduction affords (–)-dihydrodes-*N*-methylheliotridane which on dehydrogenation yields a pyrrole $C_9H_{15}N$ reducible to the (±)-dihydrodes-*N*-methyl base.[43] This base was originally compared with a number of synthetic bases theoretically derivable from the bicyclic bases (1), (2), (3) and (4), and the conclusion reached was that it has the structure (5) and that heliotridane accordingly should be formulated as (4).[10, 42, 43, 48] (±)-Heliotridane has been synthesized, see (33) → (36) below.[40]

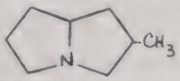
Esterification studies of the two alcoholic groups of the three related necines reveal one group to be secondary and one primary, and it is evident that the hydrogenolysable hydroxyl group owes its lability to its presence in an allylic alcohol system, which is evidently the primary alcohol, since retronecanol (which has lost this hydroxyl group) can be readily dehydrated and must accordingly be a secondary alcohol. This conclusion is confirmed by oxidation of this base to the ketone retronecanone.[4] Furthermore retronecanol contains one *C*-methyl group but retronecine does not. The two hydroxyl groups must have the 1,4 or 1,5 relationship since platynecine can be dehydrated to an internal ether, anhydroplatynecine, with a variety of reagents.[34, 50]



(1)



(2)



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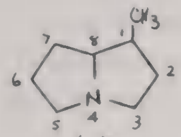
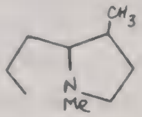


(4)

HELIOTRIDANE

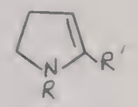


(5)

That deoxyretronecine and retronecine are not vinylamines is indicated by their stabilities and by the fact that they are weaker bases than their saturated counterparts, retronecanol and platynecine, since it has been found that vinylamines of type (6) and (7) are more basic than their saturated analogues.[8] These requirements thus lead to the structure (8) for retronecine; the alternative (9) is improbable in view of the ease with which the product of treatment of retronecanol with cyanogen bromide (10) forms an acid-stable cyclic ether (11) on treatment with alkali, and in any case can be ruled out by other evidence (see below).

Support is forthcoming for this formulation in the following ways:

1. Deoxyretronecine (12), obtained by hydrogenolytic cleavage of monocrotaline, a necic acid ester of retronecine,[11] on chlorination and reduction gives isoheliotridine (13), ozonolysis of which results in production of the amino acid (14) in which both the —$COCH_3$ and —COOH groups have been positively identified.[9]
2. Isoretronecanol (15), prepared from platynecine by benzoylation of the primary alcohol group, chlorination, reduction and hydrolysis, on oxidation gives a carboxylic acid (16), thus confirming the presence in (15) and in platynecine of a primary alcoholic group.[4]
3. A synthesis of retronecanone has been achieved as shown in (17) → (20).[7]



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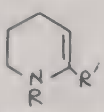

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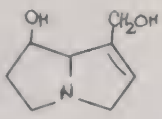

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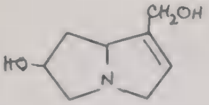

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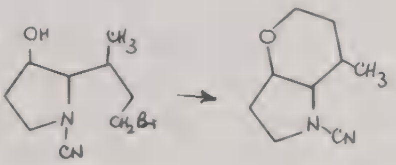
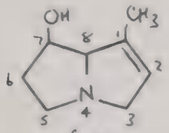
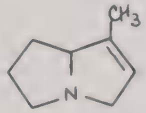


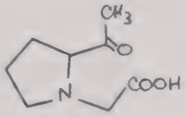
(10) (11)



(12)
DEOXYRETRONECINE



(13)
ISOHELIOTRIDINE



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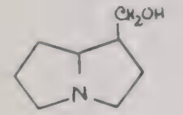
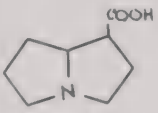


(15)
ISORETRONECANOL



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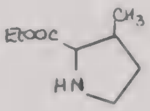
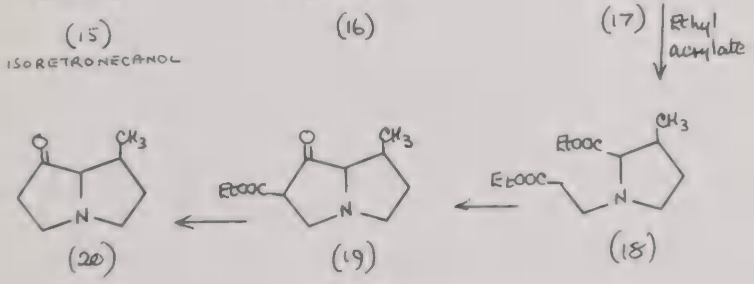


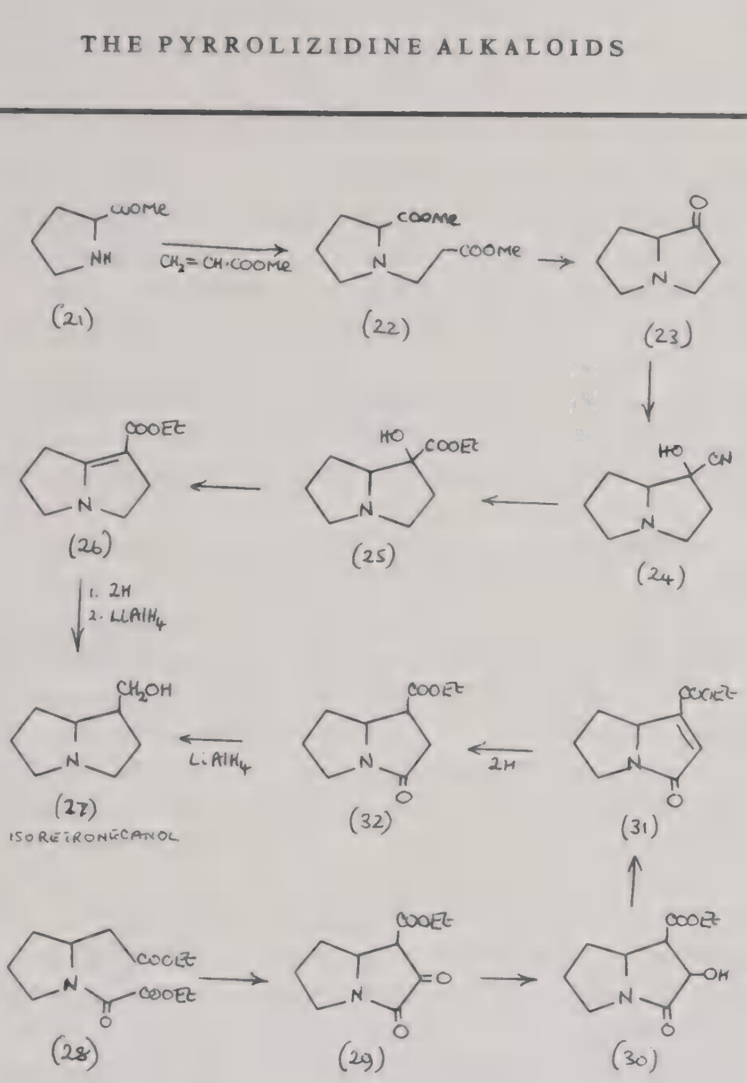


4. Two syntheses of (±)-isoretronecanol have also been accomplished; (21) → (27),[32] and (28) → (32) → (27).[49]

Trachelanthamidine, Laburnine and Lindelofidine

These three bases are all diastereoisomers of isoretronecanol (27). Trachelanthamidine is a hydroxymethylpyrrolizidine as is shown by its oxidation to a carboxylic acid which can be decarboxylated to pyrrolizidine.[44] Treatment of the base with thionyl chloride and subsequent reduction furnished an isomer of heliotridane, pseudoheliotridane[46] the racemate of which has been synthesized together with (±)-heliotridane, by the route (33) → (36).[40] This general synthesis, which is the most efficient for preparing pyrrolizidines, has been used also for the formation of one of the isomers of 1-hydroxymethylpyrrolizidine, which is identical with (±)-trachelanthimidine (37) → (40).[40] Laburnine is the enantiomorph of trachelanthamidine and lindelofidine the enantiomorph of isoretronecanol.

Supinidine, $C_8H_{13}ON$, the product of hydrolysis of the alkaloids supinine[47] and heleurine[23] is the only natural unsaturated representative of the isoretronecanol–trachelanthamidine group and, since it can be reduced over Raney nickel to isoretronecanol,[23] is Δ^1-dehydroisoretronecanol.[41]


COOMe
NH
$CH_2=CH·COOMe$
(21)
COOMe
N
COOMe
(22)
O
N
(23)
HO
CN
N
(24)
HO
COOEt
N
(25)
COOEt
N
(26)
1. 2H
2. $LiAlH_4$
CH_2OH
N
(27)
ISORETRONECANOL
$LiAlH_4$
COOEt
N
O
(32)
2H
COOEt
N
O
(31)
COOEt
N
COOEt
O
(28)
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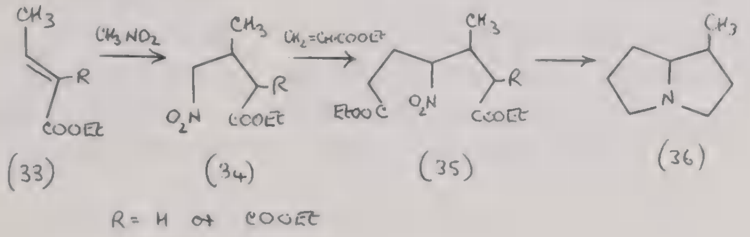
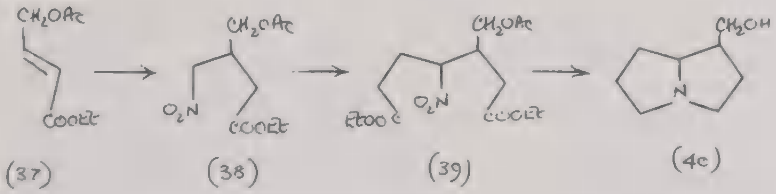
N
O
O
(29)
COOEt
OH
N
O
(30)

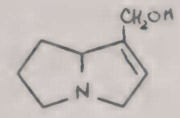

CH_3
R
COOEt
(33)
CH_3NO_2
CH_3
R
O_2N
COOEt
(34)
$CH_2=CH·COOEt$
CH_3
EtOOC
O_2N
R
COOEt
(35)
CH_3
N
(36)
R = H or COOEt


CH_2OAc
COOEt
(37)
CH_2OAc
O_2N
COOEt
(38)
CH_2OAc
EtOOC
O_2N
COOEt
(39)
CH_2OH
N
(40)

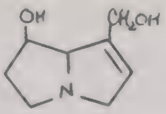
Rosmarinecine, $C_8H_{15}O_3N$, is the product of both hydrolysis and hydrogenolysis of the alkaloid rosmarinine, and must accordingly be a saturated base. It contains three hydroxyl groups and, like platynecine, can be converted into a cyclic ether (anhydrorosmarinecine) by sulphuric acid, and this compound can be transformed into anhydroplatynecine by treatment with thionyl chloride (OH → Cl) and reduction (Cl → H). Rosmarinecine is thus a hydroxyplatynecine, and the position of the additional hydroxyl group is clearly demonstrated by its production from retronecine as shown in formulae (42) → (44).[29]

STEREOCHEMISTRY OF THE NECINES

Since (±)-isoretronecanol and (±)-trachelanthamidine are related as diastereoisomeric racemates, one must have the hydrogen atoms at positions 1 and 8 *cis* and the other must have them *trans*. The ready formation and stability of anhydroplatynecine from platynecine requires the C-1 and C-8 hydrogen atoms to be in the *cis* relationship, since, as examination of models shows, it is only then that the ether ring can be closed. Thus anhydroplatynecine and platynecine must have the structures (46) and (45) or their mirror images, but the stereochemistry at C-7, although unambiguously determined in (46), cannot on this evidence alone be regarded as certain in (45) since ether formation could occur with or without inversion at this centre. However, the various interconversions show clearly that the same steric arrangement at C-1 and C-8 exists in platynecine, (−)-isoretronecanol and (−)-heliotridane; (−)-isoretronecanol and trachelanthamidine must accordingly be (47) and (48) respectively or their mirror images.[4] The mirror image structures can be ruled out since heliotridane has been shown to be (49) by three successive Hofmann degradations and reductions to (+)-3-methylheptane, the absolute stereochemistry of which is known.[52]



(41)



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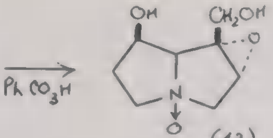

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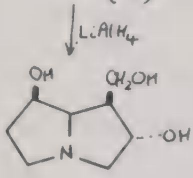
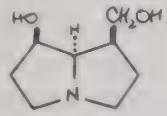
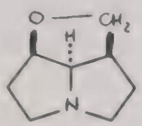


(44)
ROSMARINECINE



(45)



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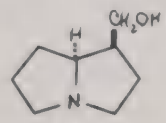

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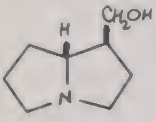

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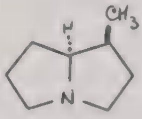

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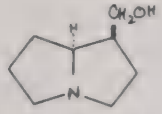
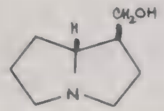
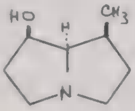


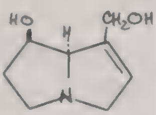
ISORETRONECANOL



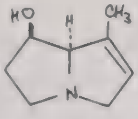
TRACHELANTHAMIDINE



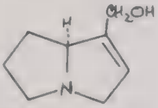
RETRONECANOL



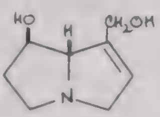
RETRONECINE



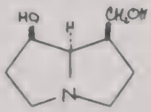
DEOXYRETRONECINE



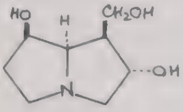
SUPINIDINE



HELIOTRIDINE



PLATYNECINE



ROSMARINECINE

The orientation of the C-7 hydrogen atom in platynecine has been determined in the following manner. Platynecine is readily converted into anhydroplatynecine, whereas dihydroxyheliotridane, which is epimeric with platynecine at C-7, resists this transformation, suggesting that the first named base has the hydroxymethyl and hydroxyl groups in the *cis* relationship, but as stated before, this argument is not in itself conclusive. However, a number of cyclic diesters of platynecine and retronecine occur naturally as alkaloids but no such cyclic esters of heliotridine (the C-7 epimer of retronecine) are known. Further, with thionyl chloride at 0° platynecine is converted into the cyclic sulphite ester (50), which can be hydrolysed back to the original base, whereas under the same conditions dihydroxyheliotridane (51) gives only chlorohydroxyheliotridane (52).[16]

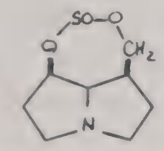
Three further necines are reported to be isomeric with platynecine and dihydroxyheliotridane[39] but little is known of their relationships.

The structures of the various necines are thus as shown opposite. (±)-Retronecine has been synthesized as shown in (53) → (64)[31] and as retronecine has been converted into platynecine, rosmarinecine, retronecanol and deoxyretronecine, this work can also be regarded as a formal synthesis of all of these bases.

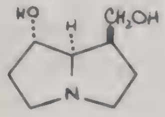
A number of alkaloids in this group appear to occur naturally as *N*-oxides, and these on hydrolysis afford the necine *N*-oxides. The oxides of trachelanthamidine, supinidine, platynecine, heliotridine, retronecine and rosmarinecine have been isolated from natural products in this way.

THE NECIC ACIDS

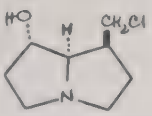
The necic acids are the esterifying acids present in the parent alkaloids, from which the necines are obtained by hydrolysis. They are not themselves necessarily the second products of hydrolysis since under the conditions of the fission they may themselves suffer cleavage, lactonization or isomerization, but the structures of the true esterifying acids may generally be easily deduced from a study of the products of hydrolysis. Acids containing 5, 6, 7, 8 and 10 carbon atoms have been clearly identified[38] and some of the most interesting examples of each type have been selected for discussion here.


SO—O
O
CH$_2$
N

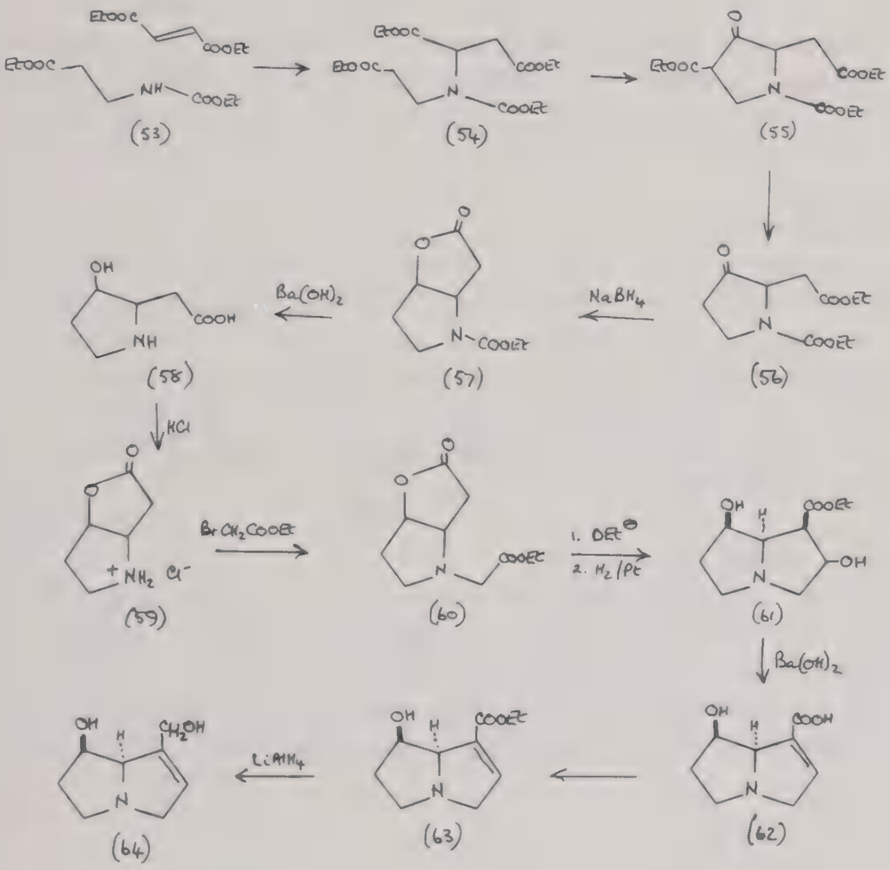
(50)


HO
H
CH$_2$OH
N

(51)


HO
H
CH$_2$Cl
N

(52)


EtOOC
COOEt
EtOOC
NH
COOEt
(53)
EtOOC
EtOOC
COOEt
N
COOEt
(54)
O
EtOOC
COOEt
N
COOEt
(55)
O
COOEt
N
COOEt
(56)
NaBH$_4$
O
O
N
COOEt
(57)
Ba(OH)$_2$
OH
COOH
NH
(58)
HCl
O
O
NH$_2$ Cl$^-$
(59)
BrCH$_2$COOEt
O
O
N
COOEt
(60)
1. OEt$^\ominus$
2. H$_2$/Pt
OH
H
COOEt
OH
N
(61)
Ba(OH)$_2$
OH
H
COOH
N
(62)
OH
H
COOEt
N
(63)
LiAlH$_4$
OH
H
CH$_2$OH
N
(64)

The C_5 Acids

These are represented by *angelic* and *sarracinic* acids. Angelic acid (65) readily isomerizes to tiglic acid (66) under conditions used for the hydrolysis of the alkaloids and care has to be taken that the correct acid is identified in each case.

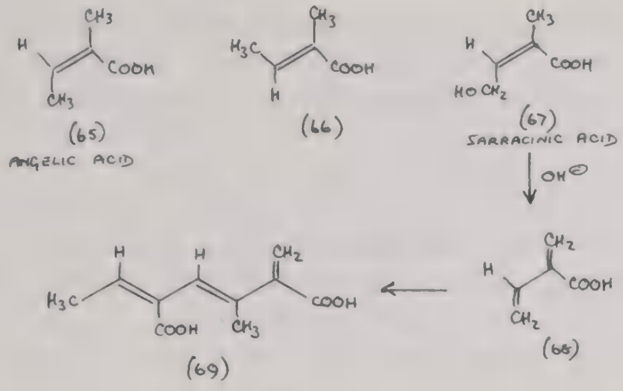
Sarracinic acid, from the alkaloid sarracine,[28] has the composition $C_5H_8O_3$ and contains one double bond, one hydroxyl and one carboxyl group. Hydrogenation affords α-methylbutyric acid (hydrogenolysis) and ozonolysis yields acetaldehyde, indicating the hydroxytiglic acid structure (67) for the acid, which has been confirmed by nuclear magnetic resonance studies.[26] Strong bases transform sarracinic acid into mikanecic acid (69) which is presumed to result from dimerization of butadiene-2-carboxylic acid (68) formed by base-catalysed dehydration of (67).[26] Mikanecic acid itself occurs naturally in the alkaloid mikanoidine.

The C_6 Acids

Dicrotalic acid, $C_6H_{10}O_5$, from the alkaloid dicrotaline, contains one hydroxyl and two carboxyl groups. It may be dehydrated through the acetyl ester or the anhydride, the final product of hydrolysis being anhydrodicrotalic acid $C_6H_8O_4$ which was found to be *cis*-β-methylglutaconic acid (70). Since the parent acid is not an α- or γ-hydroxy acid it must have the structure (71) and this was confirmed by synthesis from (72) and (73).[14]

The C_7 Acids

Trachelanthic acid, from the alkaloids trachelanthine and supinine has the composition $C_7H_{14}O_4$, is monobasic and contains two hydroxyl groups. Reductive removal of the hydroxyl groups results in ethylisopropylacetic acid (74) and oxidation affords methylisopropylglyoxal (75), leading to the structure (76) for the parent acid.[45] Trachelanthic



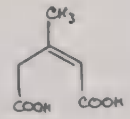
(65) ANGELIC ACID

(66)

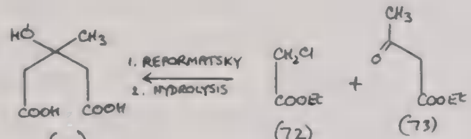
(67) SARRACINIC ACID

(68)

(69)



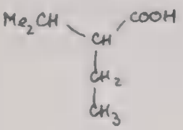
(70)



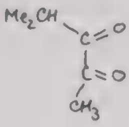
(71) DICROTALIC ACID

(72)

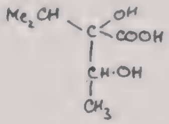
(73)



(74)



(75)



(76)

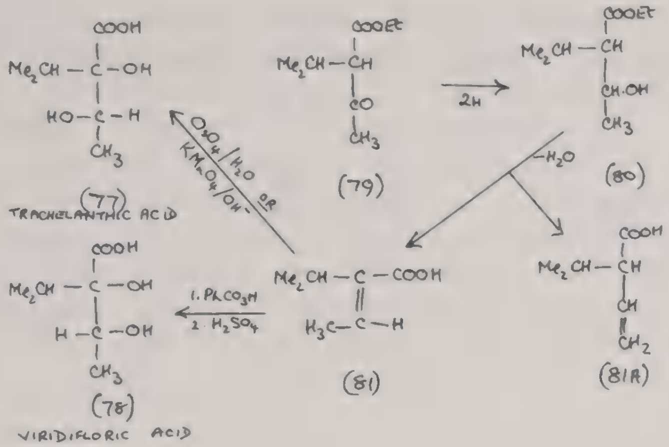
acid has been shown to be the *threo* isomer (77) and the diastereoisomeric *viridifloric acid* (from the alkaloids viridiflorine and echinatine) has the *erythro* structure (78).[30] (±)-Trachelanthic acid has been synthesized from α-isopropylcrotonic acid (81) by *cis* hydroxylation with alkaline permanganate[6] or with osmium tetroxide;[13] *trans* dihydroxylation of the same acid through the epoxide affords viridifloric acid.[13, 30] It is on the assumption that the unsaturated acid (81) [prepared together with the isomer (81A) from the keto ester (79) via the hydroxy ester (80)] is correctly formulated as β-isopropylcrotonic acid and not as α-isopropylisocrotonic acid that the assignment of the *erythro* and *threo* structures to the two dihydroxy acids rests.[30]

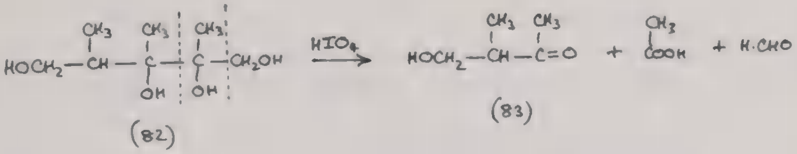
A hydroxylated trachelanthic or viridifloric acid with a $CH(OH)CMe_2$ chain in place of the isopropyl group has been isolated as *echimidinic acid*, the hydrolysis product of echimidine and heliosupine.

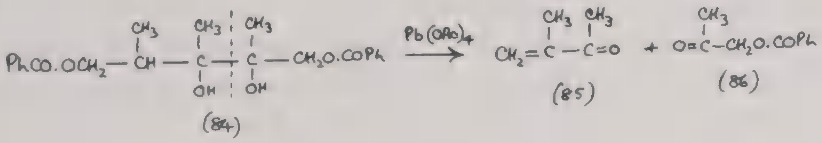
The C_8 Acids

Hydrogenolysis of the base monocrotaline affords an acid *monocrotalic acid* $C_8H_{12}O_5$, which is a lactone of the hydroxydicarboxylic acid present in the original alkaloid. The structure of the lactone was revealed in the following way. Alkaline degradation of the acid leads to carbon dioxide and monocrotic acid $C_7H_{12}O_3$ which is the product of hydrolysis of the parent alkaloid. Monocrotic acid is an oxomonocarboxylic acid oxidizable by sodium hypobromite to α,α-dimethylsuccinic acid, and can thus be formulated as α,β-dimethyllaevulinic acid (90).

Lithium aluminium hydride reduction converts monocrotalic acid into a tetrol (82) that is cleaved by periodate with the consumption of two equivalents of oxygen to give formaldehyde, acetic acid and the hydroxy ketone (83). The dibenzoyl ester of the tetrol (84) is split by lead tetraacetate to (86) and (85), also derived from benzoyl-(83). Formulation of the tetrol as (82) is thus inescapable, and monocrotalic acid,


(77)
TRACHELANTHIC ACID
(78)
VIRIDIFLORIC ACID
OsO4/H2O or KMnO4/OH⁻
1. PhCO3H
2. H2SO4
(79)
2H
(80)
−H2O
(81)
(81A)


HIO4
(82)
(83)
+ H.CHO

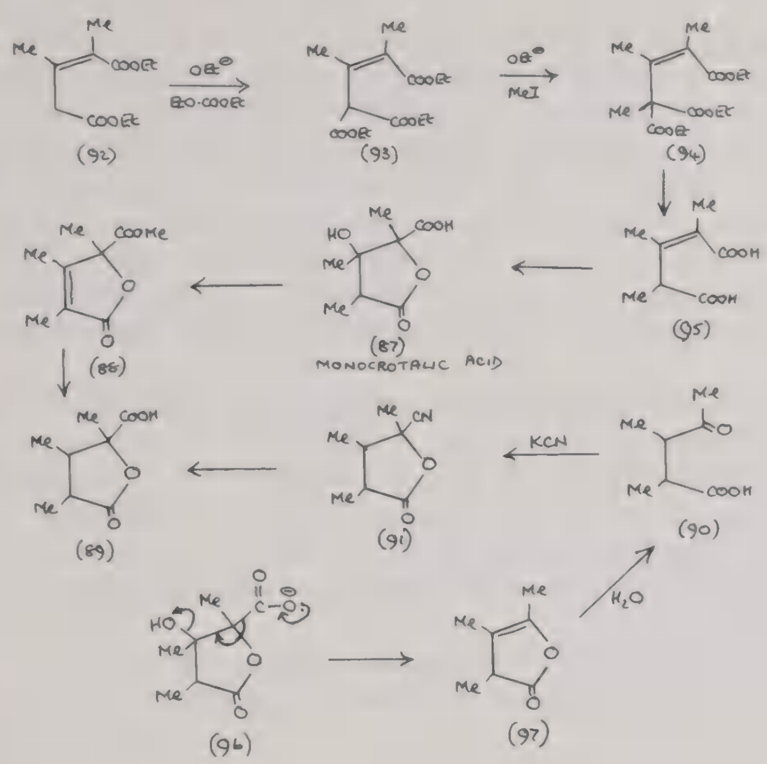

Pb(OAc)4
(84)
(85)
(86)

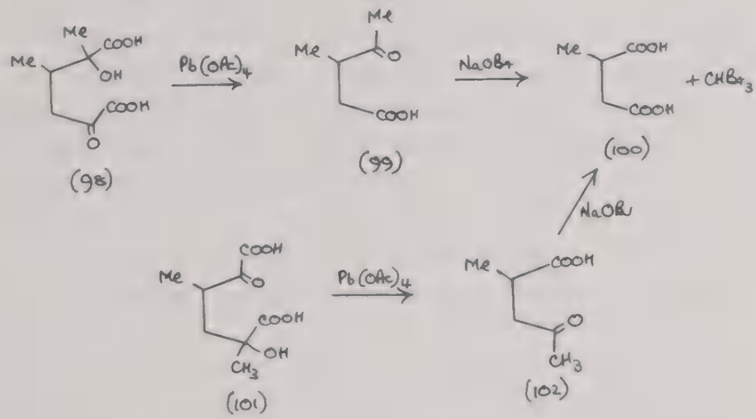
which on spectral evidence is a γ-lactone, must have the constitution (87).[3] Methyl monocrotalate may be dehydrated to methyl anhydromonocrotalate (88) and this on reduction and hydrolysis furnishes dihydroanhydromonocrotalic acid (89), the (±)- and (−)-forms of which have been prepared by synthesis from α,β-dimethyllaevulinic acid (90), via the cyanhydrin (91).[5] A synthesis of monocrotalic acid itself has also been accomplished from diethyl 2,3-dimethylglutaconate (92), via (93) and (95), *trans* dihydroxylation of which by pertungstic acid affords a mixture of diastereoisomeric racemates from which, by means of its brucine salt, monocrotalic acid (87) may be isolated; the trimethylglutaconic acid is assumed to have the geometry shown in (94).[17]

The formation of monocrotic acid (90) by alkaline degradation of monocrotalic acid may be formulated as proceeding via the enol-lactone (96) → (97).

The C_{10} Acids

Senecic and *integerrinecic acids*, the esterifying acids of the alkaloids senecionine and integerrimine, are a pair of isomeric hydroxydicarboxylic acids of compositions $C_{10}H_{16}O_5$, differing only in geometry about a double bond detectable by hydrogenation, and shown by spectroscopy to be in conjugation with one of the two carboxyl groups. Both acids can be converted into integerrinecic acid lactone from which integerrinecic acid is regenerated by cautious hydrolysis.[36] Senecic acid contains three *C*-methyl groups, one of which must be $CH_3—CH{=}C—$ since acetic acid, but no acetone or formaldehyde, is formed on permanganate oxidation of the acid, and as lactone formation does not proceed readily, it probably contains the hydroxyl group in the δ-position relative to one of the carboxyl groups. Ozonolysis of the acid yields acetaldehyde (confirming the presence of $CH_3—CH{=}C$), together with an uncharacterized product giving carbon dioxide on oxidation with lead tetraacetate, and a methyl ketone further oxidizable with sodium hypobromite to bromoform and methylsuccinic acid. Two possible structures may be advanced for the acidic ozonolysis product, (98) and (101), both leading to methylsuccinic acid (100) as end-product of this degradation, and a


(92)
OEt⊖
EtO·COOEt
(93)
OEt⊖
MeI
(94)
(95)
(87)
MONOCROTALIC ACID
(88)
(89)
(91)
KCN
(90)
H₂O
(96)
(97)


(98)
Pb(OAc)₄
(99)
NaOBr
(100)
+ CHBr₃
NaOBr
(101)
Pb(OAc)₄
(102)

distinction between the two may be made from the results of lead tetraacetate oxidation of dihydrosenecic acid. This process furnishes carbon dioxide (cleavage of an α-hydroxy acid) and an acidic methyl ketone that on sodium hypobromite oxidation is further converted into α-ethyl-γ-methylglutaric acid (103), thus fixing the relationship of the methyl and ethyl groups in the dihydro acid. Since the ethyl group in the dihydro acid must arise from the CH_3—CH=C group of senecic acid, which gives acetaldehyde on ozonolysis, (98) and not (101) must represent the second ozonolysis product and (104) must be senecic acid.[35]

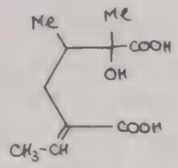
Of the isomeric pair of acids senecic acid is the less stable, being obtained from integerrinecic acid by irradiation with ultraviolet light, and on this evidence and on spectral grounds[15, 35, 36, 37] is considered to have the CH_3 and COOH groups arranged *cis* at the double bond. The absolute configuration of senecic acid at C-3 is defined as in (105) by the isolation of (+)-methylsuccinic acid (100) during the oxidation outlined above.[35, 51]

(±)-Integerrinecic, (+)-integerrinecic and (+)-senecic acids have been synthesized as shown in formulae (106) → (114).[25]

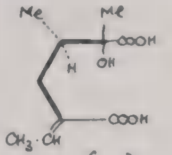
Jaconecic and Isojaconecic Acids

These two isomeric acids of composition $C_{10}H_{16}O_6$ have been obtained by the alkaline hydrolysis of the alkaloids jacobine, jaconine, and otosenine and tomentosine, but both are transformation products of the esterifying acids present in these bases. Jacobine and jaconine differ in composition by the elements of HCl, and the two bases may be interconverted by the addition or removal of these elements. Whereas alkaline hydrolysis of both bases gives retronecine + jaconecic and isojaconecic acids, prolonged boiling of each with hydrochloric acid gives retronecine + a chlorodilactone $C_{10}H_{13}O_4Cl$, which on alkaline hydrolysis gives the above two acids. These relationships are set out on the next page.

Jaconecic acid is a saturated dicarboxylic acid containing one hydroxyl group. The sixth oxygen atom cannot be detected in any functional group and was first thought to be present in an ethylene oxide system, on the basis of the presence of certain bands at 878, 1153, 1213 and 1266 cm^{-1} in the infrared spectra of jaconecic acid

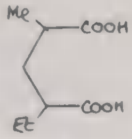


(104)

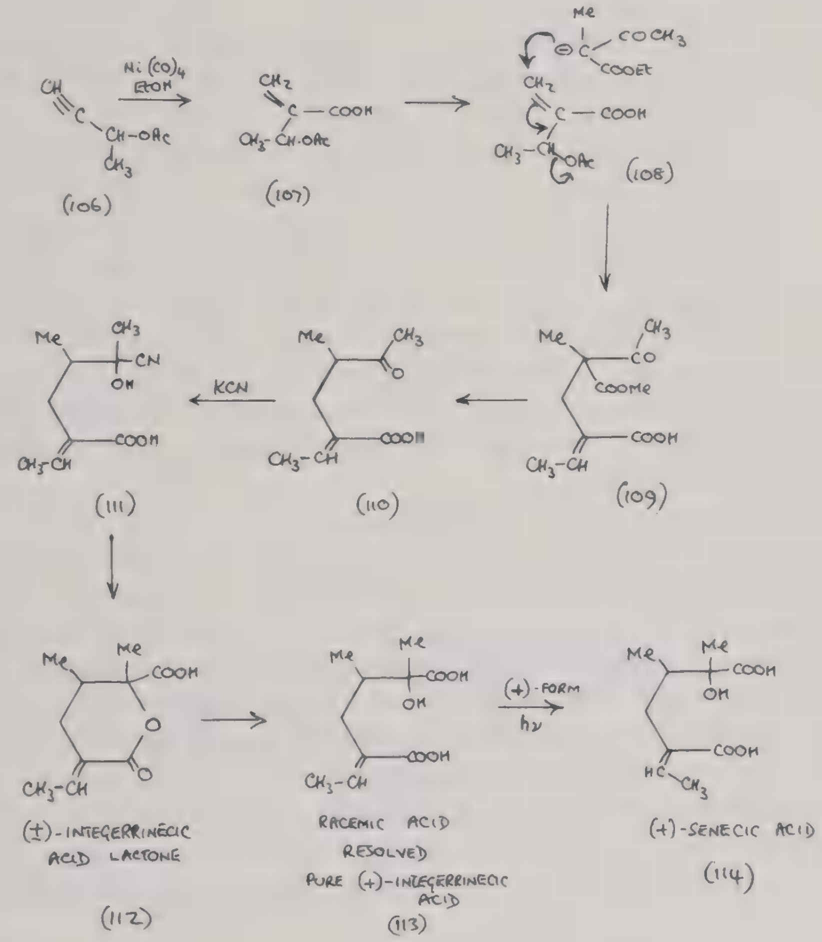


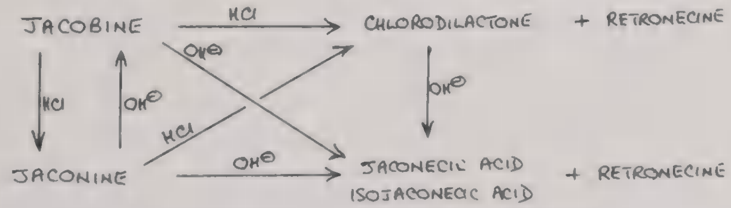
(105)

SENECIC ACID



(103)



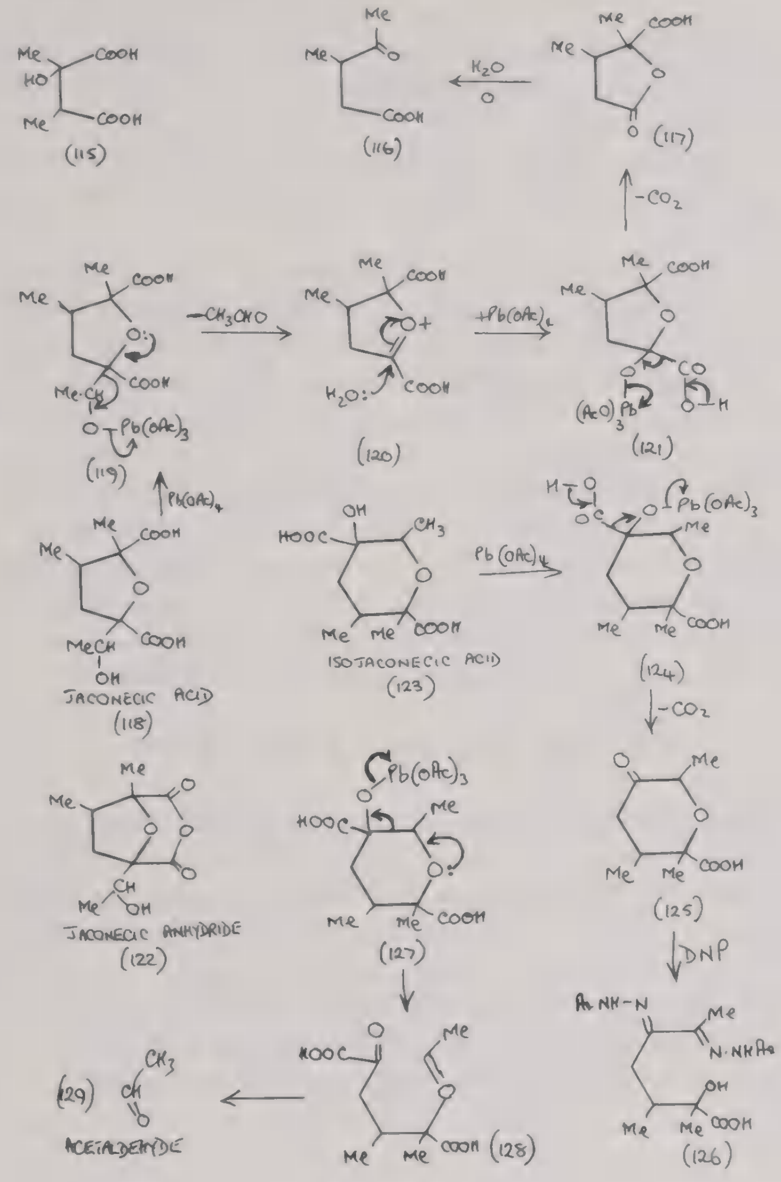


and some of its derivatives. Accordingly, jacobine and jaconine were regarded as a 1,2-epoxide and its related chlorohydrin,[22] a view that has been maintained and supported by other evidence. The inclusion of a 1,2-epoxide group in the formula of jaconecic acid which was initially suggested,[1, 20, 22] conflicts with the stability of the acid towards hydrochloric acid and catalytic hydrogenation, however, and has since been abandoned.

Both jaconecic and isojaconecic acid contain three *C*-methyl groups; the former may be oxidized with nitric acid to α,β-dimethylmalic acid (115) and two other dibasic acids ($C_9H_{14}O_6$ and $C_9H_{12}O_7$), but the latter is almost unaffected under these conditions. Jaconecic acid does not react with periodic acid at room temperature but is rapidly attacked by lead tetraacetate at 100° to give carbon dioxide, acetaldehyde, β-methyllaevulinic acid (116) and β-methyl-γ-carboxy-γ-valerolactone (117). Reduction of jaconecic acid with lithium aluminium hydride leads to a triol $C_{10}H_{20}O_4$, one hydroxyl group of which appears to be secondary, since only a bistoluenesulphonate can be obtained, from which it may be deduced that the hydroxyl group of the parent acid is also secondary; this triol is almost inert to periodic acid and accordingly cannot be an α-glycol.[21]

These facts have been combined to produce formula (118) for jaconecic acid, from which the acids (116) and (117) are obtained during lead tetraacetate oxidation as shown via (119), (120) and (121).[21] In agreement with this formulation as a substituted adipic acid, jaconecic acid forms an anhydride (122) when heated with acetic anhydride.

Isojaconecic acid is an α-hydroxy acid giving, when oxidized with lead tetraacetate, carbon dioxide, acetaldehyde and the keto acid (125), identified by conversion into the osazone (126) with 2,4-dinitrophenylhydrazine, and accordingly has been assigned the constitution (123). The elimination of acetaldehyde during the oxidation may be represented as in (123) → (127) → (128) → (129). Reduction of the dimethyl


(115)
(116)
H_2O
O
(117)
$-CO_2$
$-CH_3CHO$
$+Pb(OAc)_4$
(119)
(120)
(121)
$Pb(OAc)_4$
JACONECIC ACID
(118)
ISOJACONECIC ACID
(123)
$Pb(OAc)_4$
(124)
$-CO_2$
JACONECIC ANHYDRIDE
(122)
(127)
(125)
DNP
(129)
ACETALDEHYDE
(128)
(126)

ester of jaconecic acid with lithium aluminium hydride to the triol (130), followed by periodic acid oxidation results in the formation of formaldehyde and a ketone formulated as (131), which may be converted into an osazone (132).[21]

The structures assigned in this way to jaconecic acid and isojaconecic acid have been strongly supported by nuclear magnetic resonance studies.[21]

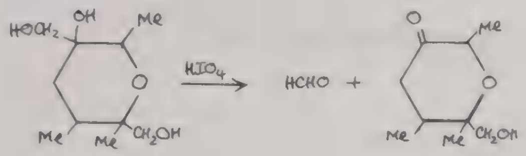
The chlorodilactone $C_{10}H_{13}O_4Cl$ obtained by the hydrochloric acid hydrolysis of jacobine and jaconine was first thought to contain two five-membered lactone rings owing to the presence of a band at 1781 cm^{-1} and the absence of bands at 1750 and 1735 cm^{-1} in the infrared spectrum,[1, 22] but it is known that δ-lactones in which there is ring strain can absorb in the 1793–1786 cm^{-1} region[19] and a study of the nuclear magnetic resonance spectrum of the dilactone and its relationship to jaconecic (135) and isojaconecic (136) acids has led to the formula (133) for the compound.[21] The two acids presumably are formed via the epoxydicarboxylic acid (134), the epoxide ring of which may be opened as in *a* to give jaconecic acid or as in *b* to give isojaconecic acid, when the dilactone is treated with alkali.[21]

TOTAL ALKALOID STRUCTURES

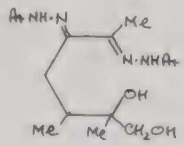
The senecio alkaloids themselves are, in general, necic acid esters of the necines, though as already pointed out the necic acids obtained by hydrolysis or hydrogenolysis may not be the true esterifying acids present in the alkaloids. The following sub-groups may be identified.

1. Monoesters of a necine and a monobasic acid.
2. Diesters of a necine and two different monobasic acids.
3. Cyclic diesters of a necine and one dibasic acid.

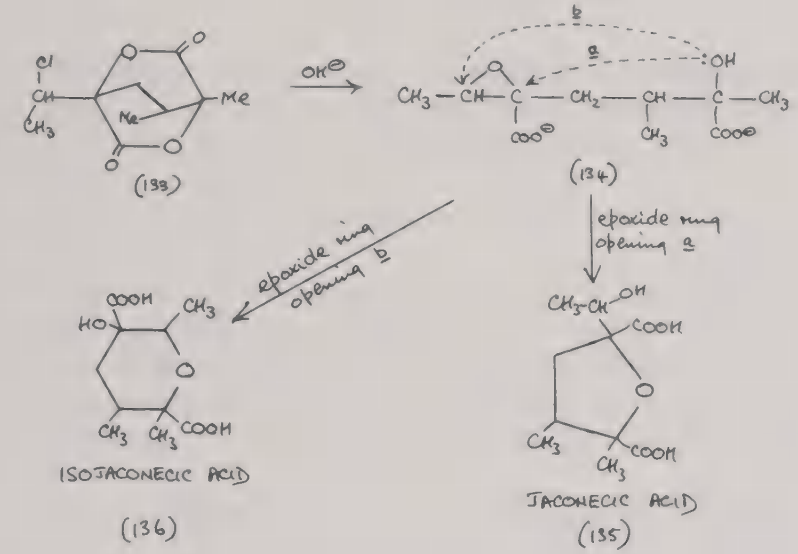
Representatives of each of these sub-groups will be presented.


HOCH₂
OH
Me
O
Me
Me
CH₂OH
HIO₄
HCHO +
O
Me
O
Me
Me
CH₂OH

(130) (131)


ArNH·N
Me
N·NHAr
OH
Me
Me
CH₂OH

(132)


Cl
CH
CH₃
O
O
Me
Me
O
O
(133)
OH⊖
b
a
:OH
CH₃ — CH — C — CH₂ — CH — C — CH₃
O
COO⊖
CH₃
COO⊖
(134)
epoxide ring opening b
epoxide ring opening a
COOH
HO
CH₃
O
CH₃
CH₃
COOH
ISOJACONECIC ACID
(136)
CH₃-CH-OH
COOH
O
CH₃
CH₃
COOH
JACONECIC ACID
(135)

1. Monoesters of a Necine and a Monobasic Acid

Echinatine This base on hydrolysis affords heliotridine and veridifloric acid. The acid, together with oxyheliotridane is obtained also on hydrogenolysis, of the alkaloid, indicating that it is the allylic alcohol of the necine that is esterified in echinatine, which is accordingly assigned the structure (137).

Trachelanthamine Hydrolysis of this base gives trachelanthic acid and trachelanthamidine, a monohydroxylic necine that can be esterified only at one point; the alkaloid thus has the structure (138).

2. Diesters of a Necine and Two Different Monobasic Acids.

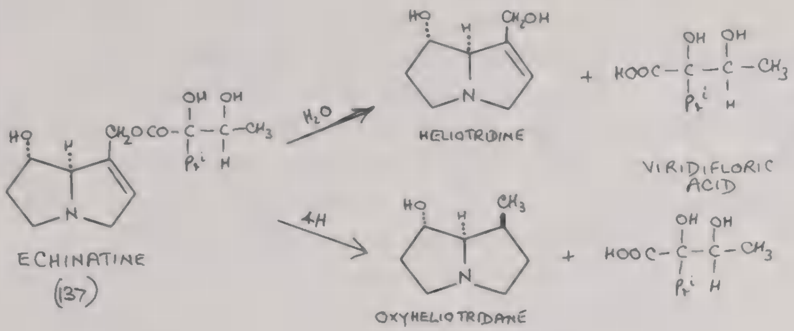
Echimidine Hydrolysis of echimidine yields retronecine and angelic and echimidinic acids whereas hydrogenolysis yields 7-(2-methylbutyryl)retronecanol (140) and echimidinic acid, showing that echimidinic acid is the esterifying acid of the allylic alcoholic group of the necine, and the alkaloid is seen to have the formula (139).[24]

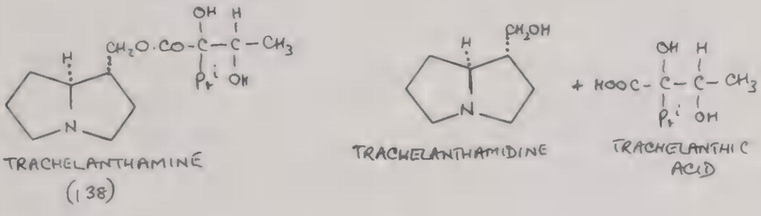
Sarracine Hydrolysis of this alkaloid affords angelic and sarracinic acids and platynecine, and since this is a saturated necine, the positions of the two acid residues cannot be determined by hydrogenolysis of the alkaloid. However, when hydrolysis is carried out under carefully controlled conditions it is found that sarracinic acid is liberated first and this acid is presumably esterifying the primary alcoholic group in the parent alkaloid, which is thus given the constitution (141).[26]

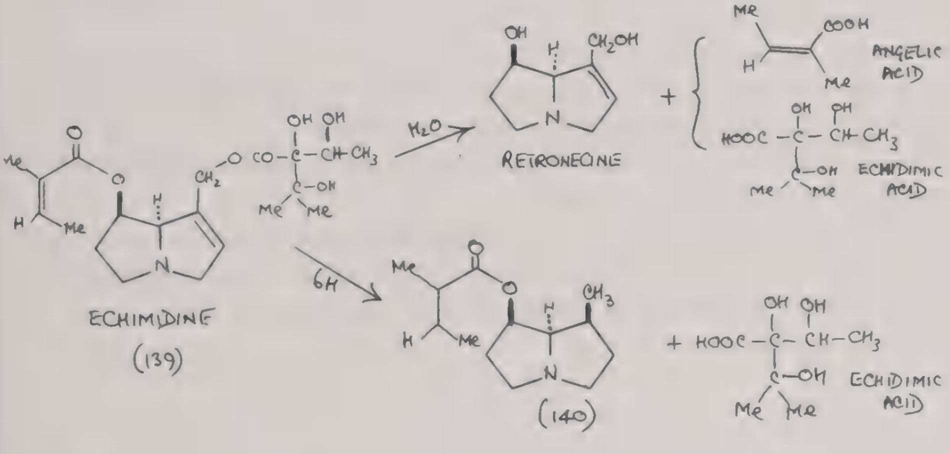
In all cases so far elucidated where two necic residues are present in the same alkaloid the one present at position 7 of the necine is angelic acid.

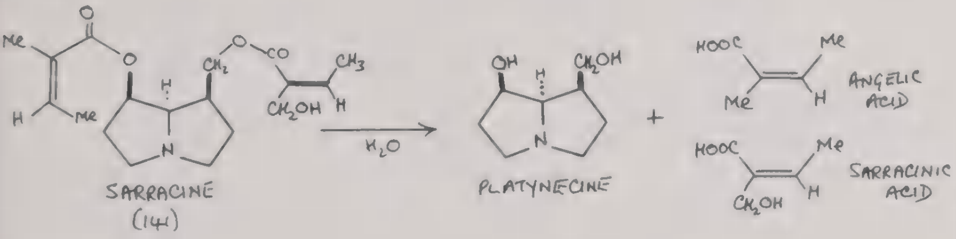
3. Cyclic Esters of a Necine and One Dibasic Acid

Monocrotaline As indicated previously, hydrogenolysis of monocrotaline gives monocrotalic acid (87) and alkaline hydrolysis gives monocrotic acid (90). Neither of these acids, however, can be the


ECHINATINE
(137)
H₂O
HELIOTRIDINE
VIRIDIFLORIC ACID
4H
OXYHELIOTRIDANE


TRACHELANTHAMINE
(138)
TRACHELANTHAMIDINE
TRACHELANTHIC ACID

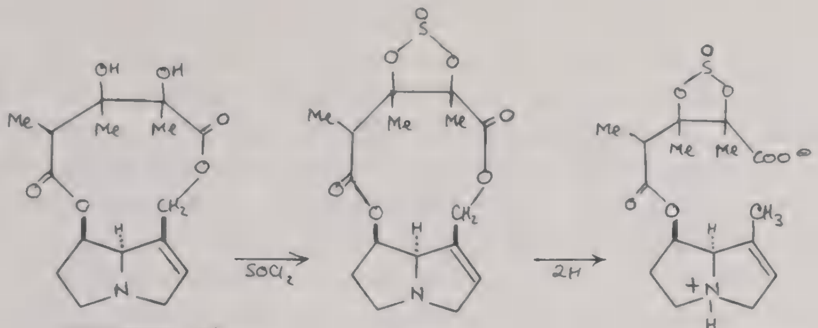

ECHIMIDINE
(139)
H₂O
RETRONECINE
ANGELIC ACID
ECHIDIMIC ACID
6H
(140)
ECHIDIMIC ACID


SARRACINE
(141)
H₂O
PLATYNECINE
ANGELIC ACID
SARRACINIC ACID

esterifying acid in the alkaloid since the infrared spectrum of monocrotaline shows a single broad ester carbonyl band at 1725 cm^{-1} with a shoulder at 1737 cm^{-1}, compared with the characteristic γ-lactone carbonyl band within the range 1774–1782 cm^{-1} in the spectra of monocrotalic acid and its derivatives. Such a spectrum for the alkaloid is in accordance with a cyclic ester structure involving the hydroxy acid corresponding to the lactone monocrotalic acid.[12]

The alkaloid with thionyl chloride forms monocrotaline sulphite (143) (proving the presence of a vicinal diol system in the base) which on hydrogenolysis affords the amino acid dihydromonocrotaline sulphite (144). This amino acid shows an infrared-absorption band at 1736 cm^{-1} and clearly contains no γ-lactone system, demonstrating that the original alkaloid had the necic acid joined by ester linkages to the necine at position 7 and at the —CH_2OH group. The production of monocrotalic acid from the alkaloid by hydrogenolysis must be due to cleavage of the allylic ester system followed by transesterification between the remaining ester group and the γ-hydroxyl group; when this hydroxyl group is bound up as in the sulphite (144) the ester is stable. Thus the carboxyl group that appears free in monocrotalic acid must be bound to the allylic CH_2OH of the necine in monocrotaline, and the lactone carbonyl of the acid must be linked to the C_7—OH group in the alkaloid, which is thus seen to have the structure (142). This is confirmed by fission of monocrotaline by lead tetraacetate with the production of pyruvic acid.[12]

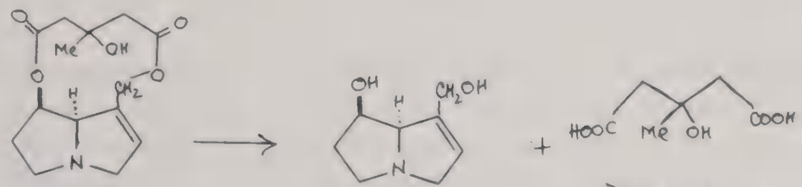
The alkaloid dicrotaline, which yields retronecine and dicrotalic acid on hydrolysis, is also a cyclic ester, but as dicrotalic acid is symmetrical only one arrangement is possible, and the alkaloid must have the structure given opposite.



MONOCROTALINE (142)

(143)

(144)



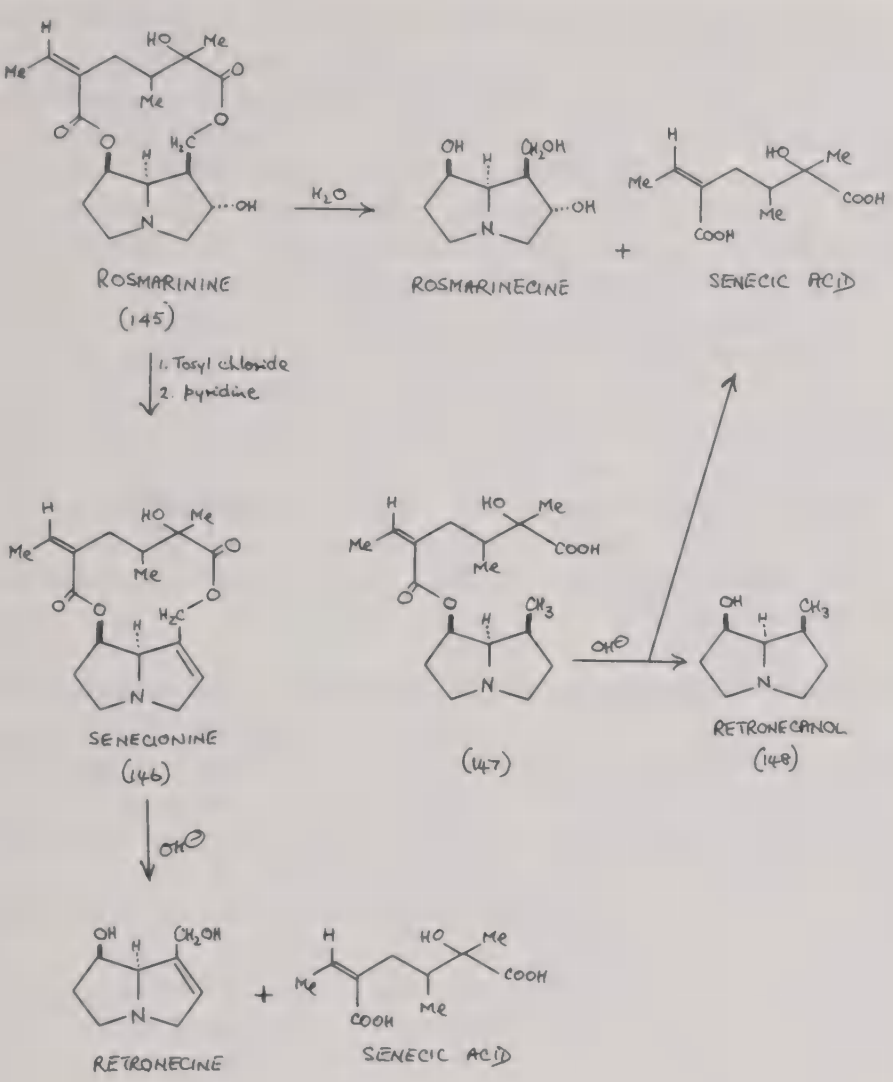
DICROTALINE

RETRONECINE

DICROTALIC ACID

Rosmarinine This alkaloid on hydrolysis furnishes rosmarinecine and senecic acid. The C-2 hydroxyl group of the necine must exist unesterified in the alkaloid since the *p*-toluenesulphonyl ester of rosmarinine when heated under reflux with pyridine gives senecionine,[33] which is another known alkaloid of this group and can be hydrolysed to senecic acid and retronecine. Senecionine can be hydrogenolysed to tetrahydrosenecionine, (147) hydrolysable to retronecanol (148) and senecic acid, showing that the necine is esterified on both hydroxyl groups. By analogy with other alkaloids of the group, senecionine (146) is formulated with the primary alcoholic group esterified by the carboxyl group of the acid likely to have the stronger ionization constant;[2] rosmarinine is thus seen to be (145).

Jacobine, jaconine and jacoline The ready interconversion of jacobine and jaconine by the addition and removal of the elements of hydrochloric acid contrasted with the stability of jaconecic and isojaconecic acids indicates that these acids cannot be the esterifying acids of the alkaloids. That these are cyclic esters of retronecine is shown by the facts that jacobine can be hydrolysed to retronecine and hydrogenolysed to an ester of retronecanol that gives jaconecic acid, isojaconecic acid and retronecanol on hydrolysis. The ready interconversion of jacobine and jaconine obviously indicates that the former is a 1,2-epoxide and the latter the related chlorohydrin, and as both on



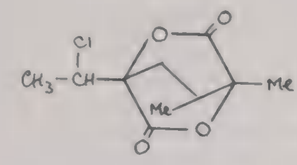
ROSMARININE
(145)
H₂O
ROSMARINECINE
+
SENECIC ACID
1. Tosyl chloride
2. pyridine
SENECIONINE
(146)
(147)
OH⊖
RETRONECANOL
(148)
OH⊖
RETRONECINE
+
SENECIC ACID

prolonged boiling with hydrochloric acid afford the chlorodilactone (149) the esterifying acids of the two alkaloids must logically be (150) in jaconine and (151) in jacobine. Hydrolysis of either base with hydrochloric acid gives first the chlorhydrin (150) which lactonizes to (149), whereas with alkali both cases (and the chlorodilactone) give the epoxide (151) and this, as shown in formulae (133)–(136), is further transformed into jaconecic and isojaconecic acids. The acid (151) has the structure of an epoxide of senecic acid, and jacobine may be formulated as an epoxide of senecionine and given the structure (152), jaconine thus becomes (153).[21] Jacobine can be hydrolysed with 25% sulphuric acid to the alkaloid jacoline which is the related glycol (154) and gives acetaldehyde on oxidation with periodic acid; obtained in this way at the same time as jacoline is a neutral substance that may be acetylated to acetyljacolinecic acid dilactone, presumably having the structure (149, Cl=OAc).[21] A bromo analogue of jaconine (153, Cl=Br) has been prepared by hydrolysis of the 1,2-epoxide of jacobine with hydrobromic acid.[21]

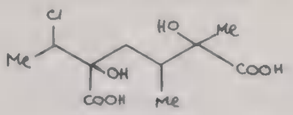
Retusamine, otosenine, renardine and onetine These four alkaloids are all closely related esters of otonecine, the structure of which has never been elucidated by chemical methods, although it is known to contain an *N*-methyl group. X-ray studies of retusamine have led to the proposal[53] of the structure (155) for this alkaloid in the form of its salt, the free base presumably being a resonance hybrid of the canonical forms (156) and (157). Otonecine must thus be a hybrid of forms (158) and (159).

The structure proposed for renardine is that of the olefin (160) whereas otosenine and otenine appear to be the related epoxide and vicinal diol respectively.

(–)-1-Methylenepyrrolizidine (161), which may be regarded as a dehydrated trachelanthamidine, has been found as a naturally occuring alkaloid in *Crotolaria damarensis* Engl. and the same base partially racemized in *C. anagyroides* H.B. and K.[27]



(149)



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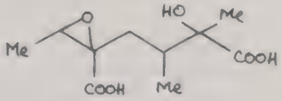

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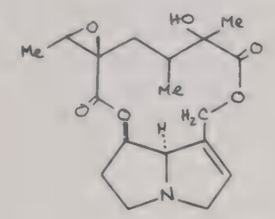
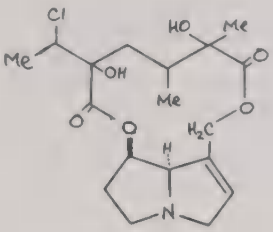


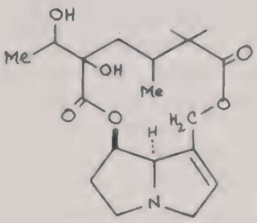
JACOBINE

(152)



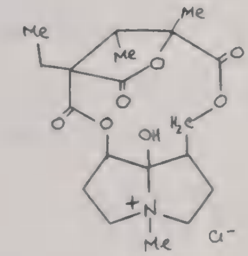
JACONINE

(153)



JACOLINE

(154)



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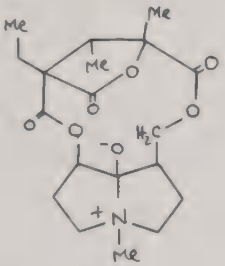

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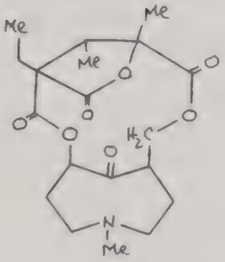

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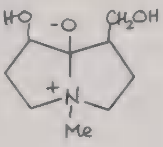

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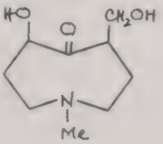

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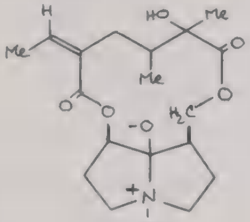

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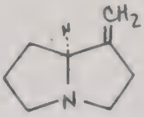

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CHAPTER 4

ALKALOIDS OF THE AMARYLLIDACEAE

Numerous alkaloids have been isolated from plants of the *Amaryllidaceae*, especially from various *Narcissus*, *Crinum*, *Haemanthus*, *Galanthus*, *Lycoris* and *Nerine* species, and the bases isolated in this way are all structurally related, being probably derived from the same precursors. A full account of the alkaloids has been published.[6, 52] At present seven groups of bases may be distinguished as exemplified by the following:

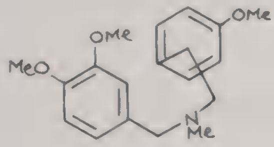
1. *N*-Benzyl-*N*-β-phenylethylamines e.g. belladine (1).
2. Derivatives of dibenzofuran, e.g. galanthamine (2).
3. Derivatives of 5,10b-ethanophenanthridine, e.g. crinine (3).
4. Derivatives of pyrrolophenanthridine, e.g. lycorine (4).
5. Derivatives of [2]benzopyrano[3, 4-*g*]indole, e.g. lycorenine (5).
6. Derivatives of [2]benzopyrano[3,4-*c*]indole, e.g. tazettine (6).
7. Derivatives of 5,11-methanomorphanthridine, e.g. coccinine (7).

All these bases may be regarded as further transformation products of suitably hydroxylated *N*-benzyl-*N*-β-phenylethylamines or of a member of one of the other groups, and indeed some of these transformations have been accomplished in the laboratory, as set out below in the more detailed descriptions of the individual groups, which form convenient divisions for discussion.

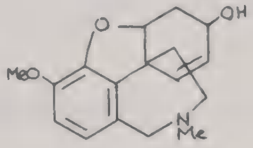
N-BENZYL-*N*-β-PHENYLETHYLAMINES

Belladine (1)

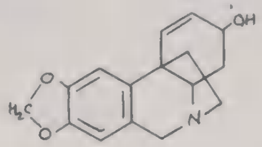
This base, from *Amaryllis belladonna* and *Brunsvigia gigantea*, has the composition $C_{19}H_{25}O_3N$, and contains three methoxyl groups and



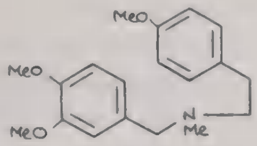
BELLADINE
(1A)



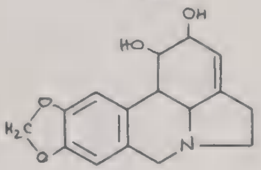
GALANTHAMINE
(2)



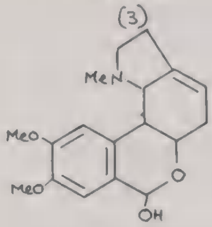
CRININE
(3)



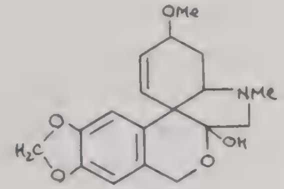
BELLADINE
(1)



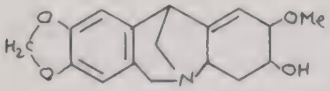
LYCORINE
(4)



LYCORENINE
(5)



TAZETTINE
(6)



COCCININE
(7)

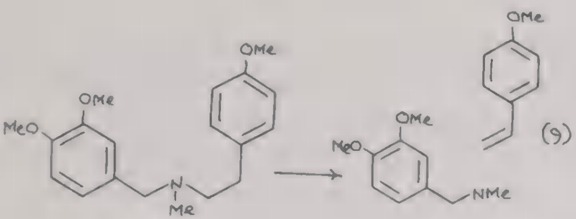
one *N*-methyl group. On Hofmann degradation it affords *N,N*-dimethylveratrylamine (8) and *p*-methoxystyrene (9) indicating, since belladine contains no C—CH_3 group and cannot therefore be an α-phenylethylamine, the structure (1) for the alkaloid.[47] By the radioactive tracer technique norbelladine (the trihydroxy analogue of 1), when fed to the appropriate plants, has been shown to act as a precursor of galanthamine (2), lycorine (4) and certain other bases of groups 2, 4, and 5 (see also Chapter 10) and in the laboratory has been converted into narwedine (10).[1] For a synthesis of belladine see formulae (29) → (33) below.[1]

DERIVATIVES OF DIBENZOFURAN

Galanthamine (2), Lycoramine

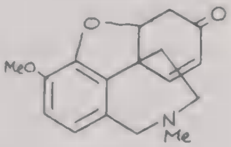
Galanthamine, $C_{17}H_{21}O_3N$, is found in a wide variety of species of *Galanthus*, especially in *G. elivesii*, in which it was first found. It contains one methoxyl, one alcoholic hydroxyl and one *N*-methyl group and one double bond, saturation of which gives dihydrogalanthamine, identical with the alkaloid lycoramine.[44] These two bases differ markedly in behaviour towards concentrated mineral acid. At 100° in glacial acetic and hydrobromic acids dihydrogalanthamine suffers demethylation and replacement of the secondary alcoholic hydroxyl by bromine, the product being a monohydric phenol that can be reduced (C—Br → C—H) and methylated to deoxylycoramine; the third oxygen atom is unaffected, presumably being part of a cyclic ether system.[45]

Galanthamine, on the other hand, affords apogalanthamine monomethylether and apogalanthamine, $C_{16}H_{17}O_2N$, both oxygen atoms of which are present in phenolic hydroxyl groups. The composition of this base indicates the presence of a second aromatic nucleus in addition to that present in the parent alkaloid, presumably the result of dehydration of the secondary alcoholic group and elimination of the ether system. Emde degradation of apogalanthamine dimethylether yields a base $C_{19}H_{25}O_2N$ that can be oxidized by permanganate to galanthamic acid $C_{16}H_{14}O_6$ (11) and an acid $C_{16}H_{16}O_4$ (12), the structures of which have been proved by synthesis.[28] Apogalanthamine itself contains no C—CH_3 group so the methyl group of the acid (12) must be produced during the Emde degradation and the product of this must thus be formulated as (13), and apogalanthamine must be (14). This

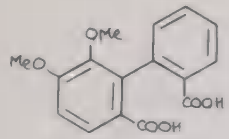


BELLADINE (1)

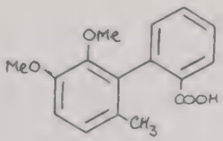
(8)



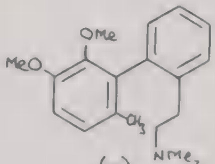
NARWEDINE (10)



(11)



(12)

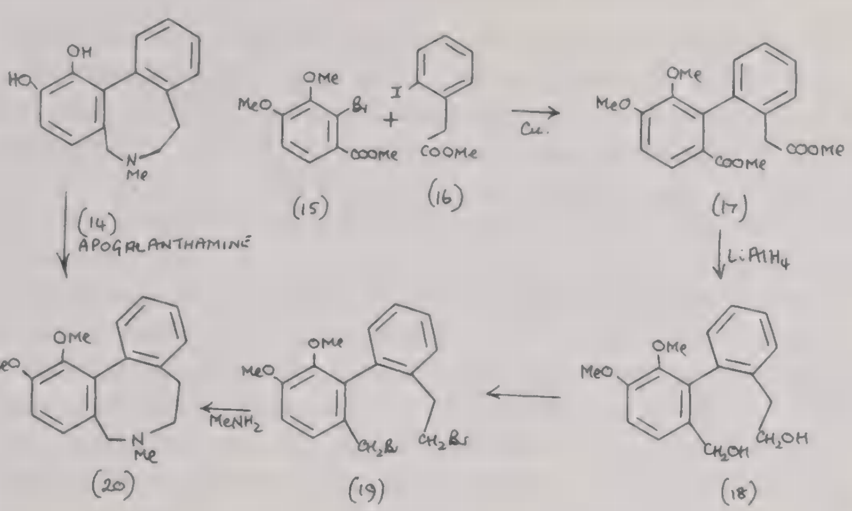


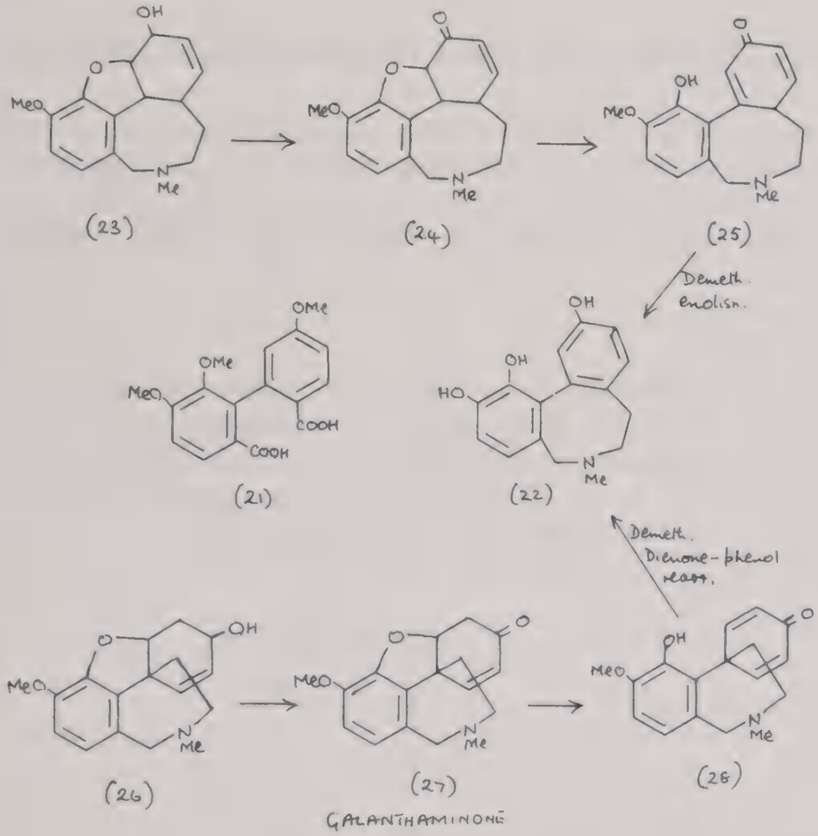
(13)

formula has been confirmed by the synthesis of apogalanthamine dimethyl ether as shown in (15) → (20).[28]

Information concerning the position of the secondary alcoholic group in galanthamine is provided by the oxidation of the alkaloid to the α,β-unsaturated ketone galanthaminone by manganese dioxide,[8] showing that the alcoholic group is allylic, and by the acid-catalysed rearrangement of this ketone to hydroxyapogalanthamine. Methylation of this base gives a trimethyl ether, Emde degradation and subsequent oxidation of which leads to the dicarboxylic acid (21), from which it is clear that hydroxyapogalanthamine has the constitution (22) and that in galanthamine the alcoholic hydroxyl group is in the 1,4 relationship to the nitrogen-bearing chain. On this evidence two structures are possible for the alkaloid (23) and (26). These two formulae result in the structures (24) and (27) respectively for galanthaminone, hydroxyapogalanthamine being obtained by α-elimination, demethylation and enolization (24) → (25) → (22), or by β-elimination, demethylation and dienone–phenol rearrangement (27) → (28) → (22); in such a dienone–phenol rearrangement the aryl group would be expected to migrate in preference to the β-nitrogen-containing aliphatic side chain.

Of these structures (23) can be eliminated since the formation by galanthaminone of a piperonylidene derivative indicates that this ketone contains the system $\text{—CH}_2\text{—CO—}$ and must have the structure (27); galanthamine must accordingly be formulated as (26) and lycoramine as its dihydro derivative.[42] The alkaloid narwedine has been shown to be identical with galanthaminone.[2] This base is very readily racemized, even on recrystallisation, presumably by a reversible conversion into the symmetrical dienone (28), and the specific rotation of narwedine is therefore dependent on the isolation procedure.[1]


OH
HO
N
Me
(14)
APOGALANTHAMINE
OMe
MeO
Br
COOMe
(15)
+
I
COOMe
(16)
Cu.
OMe
MeO
COOMe
COOMe
(17)
LiAlH4
OMe
MeO
CH2OH
CH2OH
(18)
OMe
MeO
CH2Br
CH2Br
(19)
MeNH2
OMe
MeO
N
Me
(20)


OH
O
MeO
N
Me
(23)
O
O
MeO
N
Me
(24)
O
OH
MeO
N
Me
(25)
Demeth.
enolisn.
OMe
OMe
MeO
COOH
COOH
(21)
OH
OH
HO
N
Me
(22)
Demeth.
Dienone-phenol
reactn.
O
OH
MeO
N
Me
(26)
O
O
MeO
N
Me
(27)
GALANTHAMINONE
OH
O
MeO
N
Me
(28)

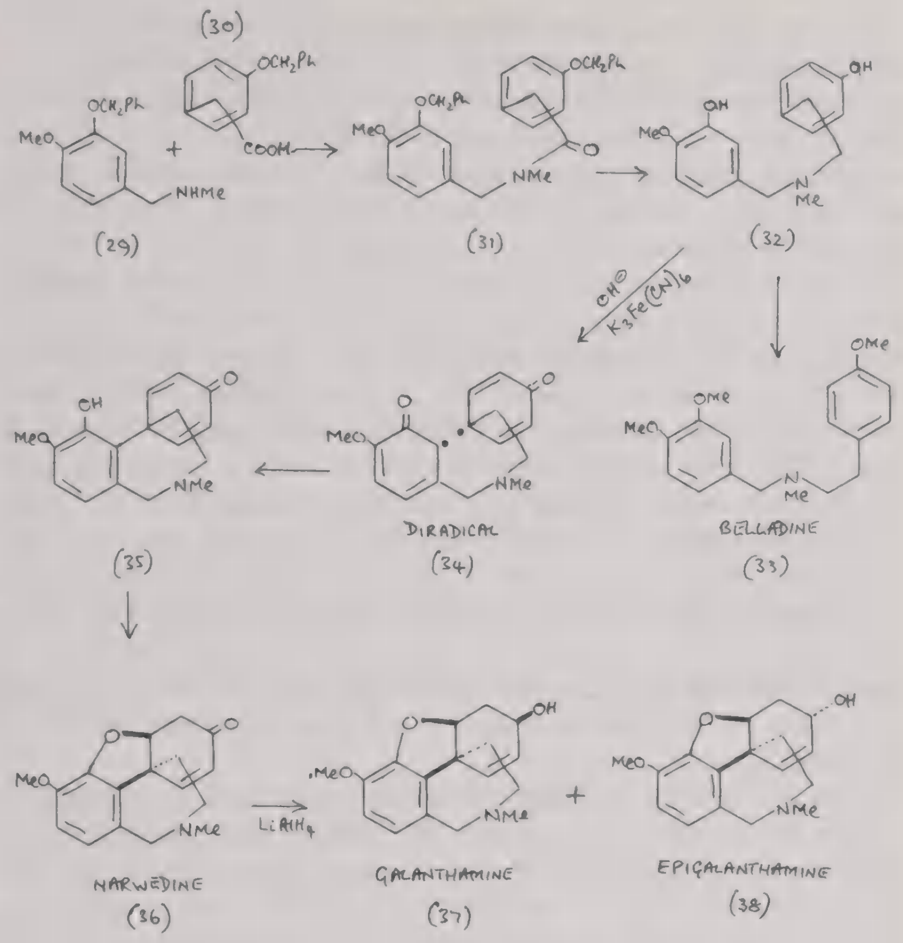
Norbelladine, narwedine, galanthamine and the epimeric epigalanthamine have been synthesized by a route (29) → (37), believed to be, in the final stages, the biogenetic route by which the last three bases arise in the plant. Oxidation of the phenol (32) by alkaline ferricyanide proceeds via the diradical (34), intramolecular coupling of which affords (35), and in this the phenol adds to the α,β-unsaturated ketone system to give ($\pm$)-narwedine. The oxide ring in (36) must have the more stable *cis* arrangement as shown since ($-$)-narwedine can be racemized but not epimerized by bases, and, as the infrared spectrum of galanthamine shows that there is hydrogen bonding between the alcoholic hydroxyl group and the oxygen atom of this ring, galanthamine and epigalanthamine must have the stereochemistry shown in (37) and 38),[1] Some evidence, based on molecular rotation differences, exists that the *absolute* configuration of ($-$)-galanthamine is as shown in (37).[1]

DERIVATIVES OF 5,10b-ETHANOPHENANTHRIDINE

The bases of this group comprise a closely interrelated series of compounds derived from both enantiomorphs of the basic ring system, a state of affairs infrequently encountered in the alkaloids. The relationships between the alkaloids have been elucidated by a number of interconversions.

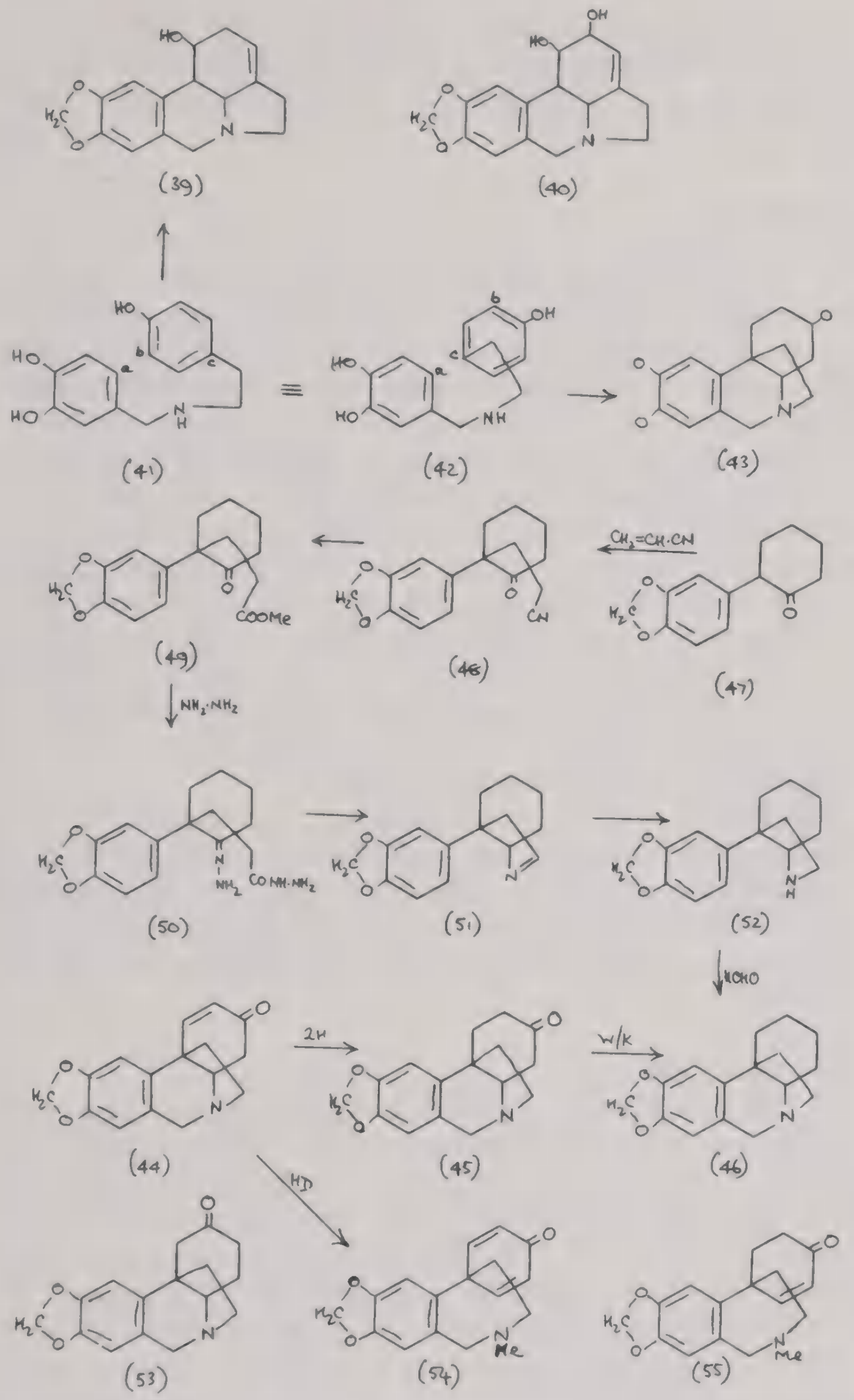
Crinine (57)

This base, isolated from a number of *Crinum* species and from *Nerine bowdenii*, has the composition $C_{16}H_{17}O_3N$, and contains a methylenedioxy group, a hydroxyl group and a reducible double bond, but no *N*-methyl group. The spectra and composition clearly indicate the presence of one aromatic nucleus. The base is isomeric with and


(30)
OCH2Ph
OCH2Ph
MeO
+
COOH
NHMe
(29)
OCH2Ph
OCH2Ph
MeO
O
NMe
(31)
OH
OH
MeO
N
Me
(32)
OH⊖
K3Fe(CN)6
OMe
OMe
MeO
N
Me
BELLADINE
(33)
OH
O
MeO
NMe
(35)
O
O
MeO
NMe
DIRADICAL
(34)
O
MeO
NMe
NARWEDINE
(36)
LiAlH4
OH
MeO
NMe
GALANTHAMINE
(37)
+
OH
MeO
NMe
EPIGALANTHAMINE
(38)

contains the same functional groups as caranine (39), and the occurrence of the latter, and of lycorine (40) in *crinum* species led at first to a suggestion that crinine and caranine possess the same carbon–nitrogen skeleton. This hypothesis could not be maintained when it was found that certain reactions characteristic of the lycorine–caranine group (see below), in particular dehydrogenation over palladium at 200° and oxidation to a phenanthridone by permanganate, could not be effected with crinine. However, the possibility of a close relationship between the two groups as a result of origin from the same type of precursor remains, and the occurrence in *Crinum* and *Lycoris* species of the alkaloid galanthamine suggested that a spiro-structure, which would readily explain the resistance to dehydrogenation, may be present in crinine. The origin of both caranine (39) and such a spiro-compound with the substitution pattern (43) can be envisaged from the same precursor (41)≡(42). Oxidative coupling of (41) at *a* and *b*, in the manner postulated above in the biogenesis of galanthamine would, after other changes, afford caranine (39), whereas coupling at *a* and *c* (42) would afford the skeleton (43), after the same types of subsequent changes. This has proved a fruitful line of reasoning and crinine has been shown to have the skeleton and substitution pattern of (43) in the following way.

Crinine is rapidly oxidized by manganese dioxide to oxocrinine, which is an α,β-unsaturated ketone (44), indicating that crinine is an allylic alcohol. Reduction of this base yields dihydrooxocrinine (45), which is converted into (–)-crinane (46) by Wolff–Kishner reduction, and the structure of crinane is established by the unambiguous synthesis (42) → (52) → (46).[50, 51] Formation of a dibenzylidene derivative by dihydrooxocrinine indicates that this base contains the system $—CH_2—CO—CH_2—$, so that only structures (45) and (53) are possible. The placing of the oxygen atom and the location of the double bond in oxocrinine, and hence in crinine, is revealed by the Hofmann degradation of oxocrinine to the optically inactive symmetrical dienone (54), the ease of the degradation establishing the β-aminoketone structure (44) for oxocrinine. Further support for this formulation is forthcoming from the facile degradation of dihydrooxocrinine (45) to the optically active α,β-unsaturated ketone (55), and the reduction of this


(39)
(40)
(41)
(42)
(43)
(49)
(48)
CH₂=CH·CN
(47)
NH₂·NH₂
(50)
(51)
(52)
HCHO
(44)
2H
(45)
W/K
(46)
HD
(53)
(54)
(55)

to the inactive saturated ketone (56) also accessible from the dienone (54).[11] The structure of crinine is accordingly uniquely defined as (57); the stereochemistry of this and other bases of the group is discussed below.

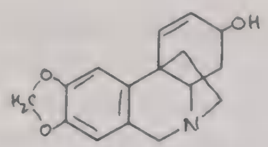
Powelline (64)

Powelline, $C_{17}H_{19}O_4N$, isolated from two *Crinum* species, contains one methoxyl group in addition to the same functional groups as crinine which it closely resembles in its reactions. In a manner analogous to the degradation of crinine to crinane it was converted through oxopowelline and dihydrooxopowelline into (+)-powellane, suggesting that powelline is an *ar*-methoxycrinine. This has been confirmed by the removal of the methoxyl group by reduction of powelline with sodium and amyl alcohol to dihydroepicrinine (58) and α- and β-crinene [an isomeric pair of olefins (59) and (60)] the last two of which on hydrogenation afford (−)-crinane (46).[12] The production of dihydroepicrinine during this process does not mean that powelline is a derivative of epicrinine, which differs from crinine only in the positions of the H and OH at the secondary alcoholic group and is the main product of complex hydride reduction of oxocrinine (44), since apparently an epimerization at this centre occurs during the reduction. The stereochemistry of powelline is discussed below.

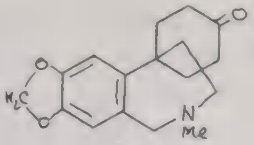
The position of the methoxyl group at C-7 is revealed by nuclear magnetic resonance studies and confirmed by sodium and liquid ammonia reduction of (+)-powellane (61) to the phenol (62), the methyl ether of which has been synthesized from (63) by a route analogous to the synthesis of crinane (46). Powelline must therefore have the structure (64).[35]

Buphanamine (68)

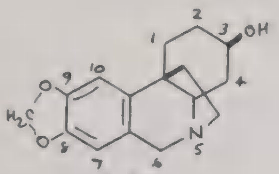
This alkaloid from two *Boöphone* species is isomeric with powelline and contains the same functional groups. Dihydrobuphanamine can be oxidized by the Oppenauer method to dihydrooxobuphanamine, isomeric with dihydrooxopowelline, which yields (+)-powellane on Wolff–Kishner reduction.[14, 51] Since dihydrooxobuphanamine gives only a monobenzylidene derivative, the keto group in this base, and hence the hydroxyl group in buphanamine, must be at C-1 or C-4. Position 4 for the hydroxyl group is ruled out by oxidation of buphanamine to



(57) CRININE

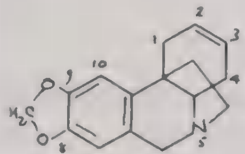


(56)



(58)

DIHYDROEPICRININE



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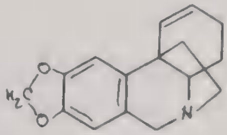

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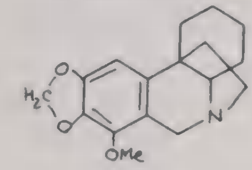
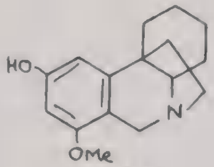
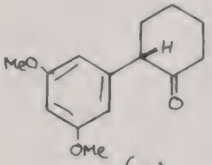


(61)

POWELLANE



(62)



(63)

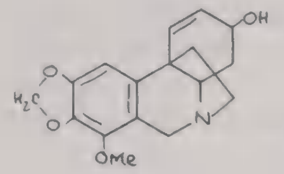
an α,β-unsaturated ketone (oxobuphanamine), which on epoxidation and subsequent successive reduction with sodium borohydride and lithium aluminium hydride gives the non-vicinal diols dihydrocrinamidine (65) and nerbowdine (66), the structures of which are known from other work (see below) not to contain a hydroxyl group at C-4.[16]

The double bond must be at 2,3 since lithium aluminium hydride reduction of oxobuphanamine, which must be (67), affords buphanamine (68) together with the epimeric epibuphanamine;[16] the assignment of the stereochemistry of the alcoholic group rests on optical rotation studies.[16]

Crinamidine (84), Undulatine (83), Nerbowdine (88)

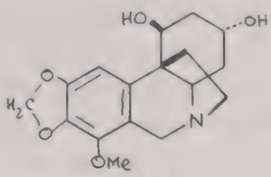
Crinamidine, a tertiary base of composition $C_{17}H_{19}O_5N$ from *Crinum moorei* and several *Nerine* species, contains one methoxyl, one methylenedioxy group and one hydroxyl group, the fifth oxygen atom apparently being present in a cyclic ether system. Undulatine $C_{18}H_{21}O_5N$, also isolated from certain *Nerine* species, contains two methoxyl groups and no hydroxyl group, but otherwise the same functional groups as crinamidine, of which it is the methyl ether, since methylation of crinamidine with methyl *p*-toluenesulphonate affords undulatine.[14]

Undulatine can be degraded to (+)-powellane (see below), thus establishing the carbon–nitrogen skeleton. With lithium aluminium hydride oxide ring reduction occurs to a mixture of two isomeric alcohols, dihydroundulatine and isodihydroundulatine, the positions of the hydroxyl groups in which represent the two points of attachment of the cyclic oxygen atom. Careful oxidation of dihydroundulatine yields the corresponding ketone oxodihydroundulatine, which is very readily epimerized by bases to the more stable isomer, a result only explicable on the assumption that the ketone contains the epimerizable system —CHR—CO— , and in this system the group R must be methoxyl since zinc/acetic acid reduction of the ketone results in loss of the methoxyl group, as does Wolff–Kishner reduction. This last reaction leads to an unsaturated base, presumably by initial elimination of methanol, which may be hydrogenated to (+)-powellane (61)[48] thus establishing the basic ring structure.



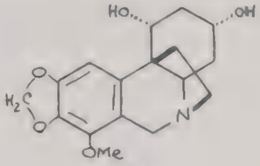
(64)

POWELLINE



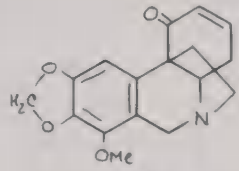
(65)

DIHYDROCRINAMIDINE

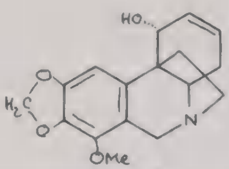


(66)

NERBOWDINE



(67)



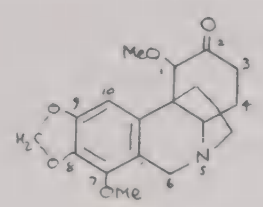
(68)

BUPHANAMINE

Deuterium exchange studies on the epimerized oxodihydroundulatine reveal the presence in this ketone of three α hydrogen atoms, so only the part structures (69) → (72) can be considered, and of these (71) and (72) with a C-3 carbonyl group can be eliminated, since desmethoxyoxodihydroundulatine (the product of reductive elimination of the methoxyl group referred to above) is not identical with oxodihydropowelline (73). The C-3 position for the methoxyl group, and hence part structure (70) for the ketone, has been demonstrated by the conversion of dihydroundulatine into a symmetrical, optically inactive base in the following way. Dehydration of dihydroundulatine via the *O*-methanesulphonate yields an olefin (74), identical with the alkaloid buphanidrine and hydrogenation of this to (75), followed by Hofmann degradation, affords a mixture from which the optically active methine base (76) can be isolated. This methine base on hydrogenation is converted into the optically inactive and therefore symmetrical dihydromethine (77); oxodihydroundulatine must therefore be (78) and dihydroundulatine (70), and one point of attachment of the cyclic oxygen atom must be C-2.[48]

The second point of attachment of the cyclic oxygen is known to be C-1 as the oxidation of isodihydroundulatine (80), the second product of lithium aluminium hydride reduction of undulatine, to oxoisodihydroundulatine (81), gives a β-methoxy ketone which very readily loses methanol under the influence of bases to yield oxobuphanamine (82)=(67). Further use of lithium aluminium deuteride for the reduction of undulatine affords a deuterated dihydroundulatine, the ketone from which must be deuterated on an α-carbon atom since it loses deuterium on enolization and therefore the oxide ring must be a 1,2-epoxide, the 2,3-epoxide structure being ruled out by the fact that isodihydroundulatine is clearly not a hemiketal.[48]

Accordingly undulatine may be assigned the structure (83) and crinamidine must be (84). Further confirmation of these assignments is obtained by the oxidation of crinamidine to oxocrinamidine (85),



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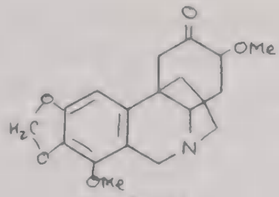

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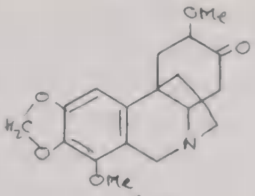

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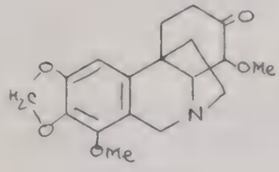

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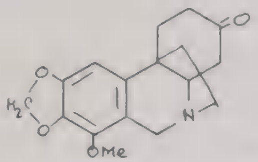

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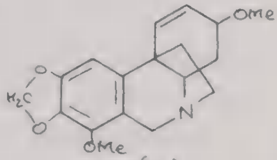

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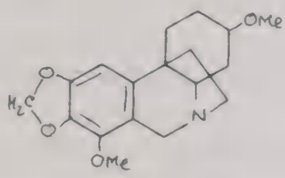

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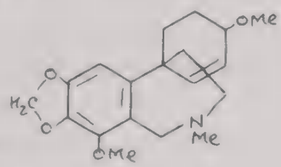

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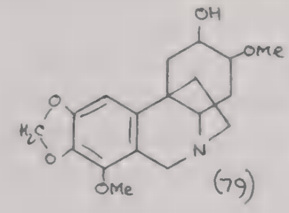

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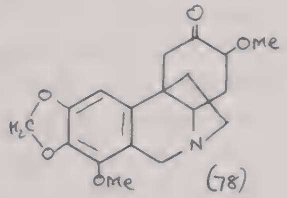

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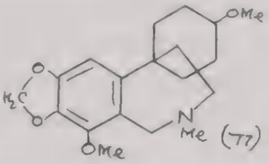

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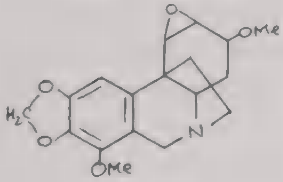
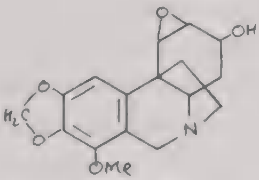


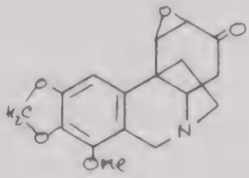
(83)

UNDULATINE



(84)

CRINAMIDINE



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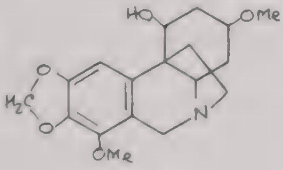

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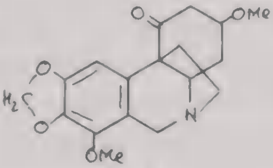

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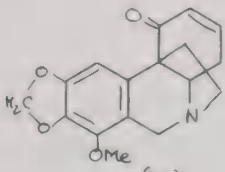


(82)

and the reduction of this epoxide with zinc and acetic acid to oxopowelline (86) and dihydrooxopowelline (87), also obtainable from powelline (64).[17] Epoxidation of oxopowelline (66) affords an epoxide diastereoisomeric with oxocrinamidine, and this with lithium aluminium hydride furnishes two diastereoisomeric non-vicinal diols (88), one of which is identical with the alkaloid nerbowdine.[15]

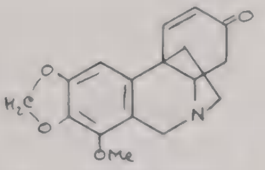
The stereochemistry of the alkaloids is discussed below.

Haemanthamine (98), Haemanthidine (107)

These two bases, isolated from a number of *Haemanthus* and other species, have the compositions $C_{17}H_{19}O_4N$ and $C_{17}H_{19}O_5N$. The elucidation of the structures of the alkaloids was originally dependent on the conversion of haemanthamine into a degradation product of the alkaloid tazettine, discussed in the next section, and on the conversion of haemanthidine into tazettine itself. More recently, however, haemanthamine has been directly related to crinine.

Haemanthamine contains one methylenedioxy, one methoxyl and one hydroxyl group and one reducible double bond. Both the alkaloid and its dihydro derivative may be oxidized to ketones, and of these oxohaemanthamine on heating with potassium t-butoxide in t-butanol is aromatized to the amino acid (91) [structure proved by synthesis (89) → (91)] and oxodihydrohaemanthamine on Hofmann degradation yields the optically active amino acid (92) which may be hydrogenated (with simultaneous hydrogenolysis) to the optically inactive neutral compound(93). The structure of this end-product rests on its preparation by the hydrogenation/hydrogenolysis of the base (94) obtained by the Hofmann degradation of dihydrotazettine (95), see below under ‘Tazettine’.

From these reactions the substitution pattern of the aromatic nucleus and the position of the methoxyl group relative to this nucleus are revealed, provided the structure of tazettine is correctly defined. The carboxyl group present in the amino acids (91) and (92) may reasonably be assumed to be derived from the carbonyl groups of oxohaemanthamine and oxodihydrohaemanthamine, and as the double bond of (92) is presumably introduced by the Hofmann degradation, the structure (96) may be advanced for oxodihydrohaemanthamine. The alternative (97) cannot be seriously considered as, unlike lycorine and related bases, no derivative of haemanthamine can be oxidized to a phenanthridone. As haemanthamine is neither an enol ether nor a blocked



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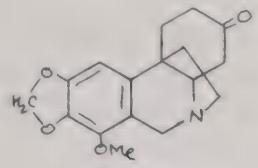

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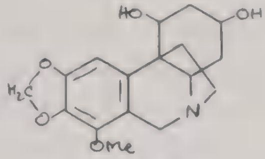
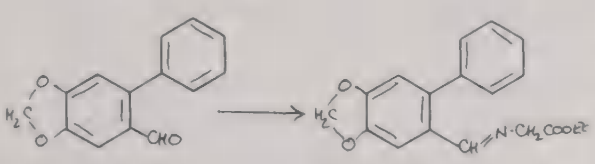
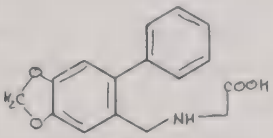


(88)
NERBOWDINE



(89) (90)



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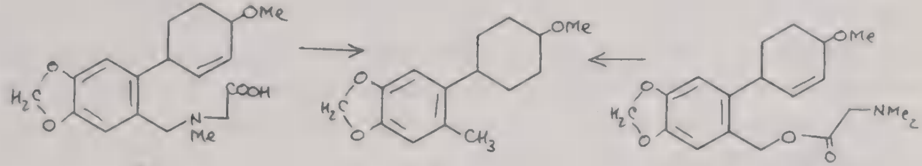
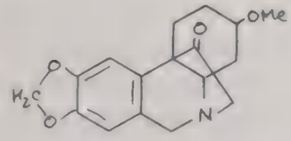


(92) (93) (94)



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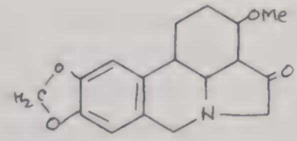

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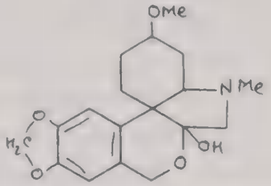


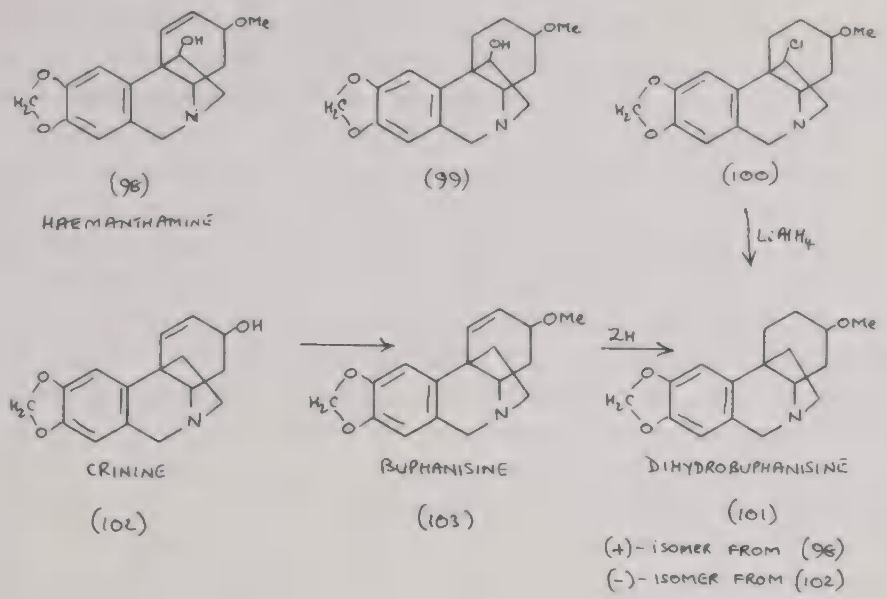
DIHYDROTAZETTINE
(95)

enamine the only position for the double bond is C-1 : C-2 and accordingly, the alkaloid must be assigned the structure (98).[18]

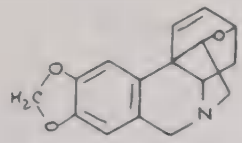
This is confirmed by the conversion of dihydrohaemanthamine (99) into the chloro compound (100) which on reduction yields (+)-dihydrobuphanisine which is the enantiomorph of (–)-dihydrobuphanisine, preparable from crinine (102)=(57) by methylation to the alkaloid buphanisine (103) and hydrogenation.[14] Haemanthamine is seen, on this evidence, to be derived from (+)-crinane enantiomorphic with (–)-crinane, on which the alkaloids discussed in the preceeding sections are based. [(+)Powellane, in spite of its dextrorotation has been quite clearly related to (–)-crinane, presumably the aromatic methoxyl group has a profound effect on the rotatory properties].

Haemanthamine is converted by dilute hydrochloric acid into a non-hydroxylic cyclic ether, apohaemanthamine (104), but dihydrohaemanthamine, which is not an allylic ether and would not be expected to undergo hydrolysis as easily as the parent alkaloid, is stable under these conditions; the dihydroapo base (105) can, however, be prepared by catalytic reduction of (104).[13]

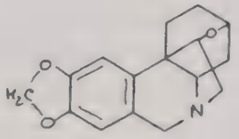
Haemanthidine contains the same functional groups as haemanthamine with an additional hydroxyl group. Dilute acid converts the base into the non-hydroxylic ether apohaemanthidine, reducible to dihydroapohaemanthidine, and the hydroxyl group may be removed from this by treatment with thionyl chloride and subsequent reduction with lithium aluminium hydride, the end-product being apohaemanthamine. The carbon–nitrogen skeleton of the alkaloid is thus the same as that of haemanthamine, of which it must be a hydroxy derivative. Since haemanthidine is not a phenol, an enol or a hemiketal, it must bear the additional hydroxyl group at one of the positions 4, 4a, 6 or 12 in formula (106), but the oxidation of the alkaloid, its dihydro derivative and apohaemanthidine to compounds containing a carbonyl group conjugated with the aromatic nucleus (infrared absorption at 5·88–5·90μ),



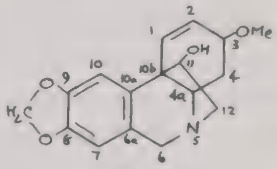
(+)- isomer from (98)
(−)- isomer from (102)



(104)



(105)



(106)

shows that the complete structure of the base must be (107).[43] These three carbonyl compounds would be expected to behave like ketones and not like amides, since in, for example, oxoapohaemanthidine (108) the canonical structure (109), which violates Bredt's rule, would be expected to make a negligible contribution to the normal state of the molecule. In fact all three carbonyl compounds show ketonic rather than amide absorption in the infrared, and all are reduced to the parent alcohols by sodium borohydride; however no oximes are obtainable and cleavage to amino acids takes place quite readily.[13]

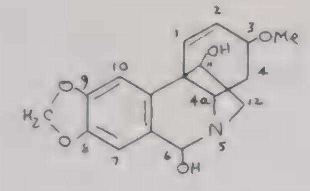
Haemanthidine (107) is very readily converted into tazettine by formaldehyde and formic acid or methyl iodide, and to nortazettine by dilute bases. During this process the oxidation state of C-11 is increased and that of C-6 is decreased, and a plausible process involves equilibrium conversion of the carbinolamine (107) into the aldehyde 110, R = H or Me), hydride transfer in this, (111) → (112), or in the hemiacetal (114), to give tazettine (113, R = Me), or nortazettine (113, R = H). With nitrous acid haemanthidine (107) yields the *N*-nitroso-hemiacetal (114, R = NO) which may be oxidized to the lactone (115), and also transformed into *N*-nitrosonortazettine (113, R = NO). Attempts to rearrange 11-acetylhaemanthidine methiodide with base affords only *O*-acetyl-110, R = Me).[43]

The alkaloids crinamine[13] and 6-hydroxycrinamine[9] are the C-3 epimers of haemanthamine and haemanthidine; 6-hydroxycrinamine can be transformed into crinelline the C-3 epimer of tazettine.[9]

STEREOCHEMISTRY OF THE 5,10b-ETHANOPHENANTRIDINE BASES

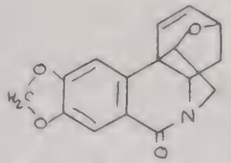
The structures of the alkaloids given above have been presented with only occasion reference to stereochemistry, but the relative stereochemistry of the bases is now known, though the absolute stereochemistry has not yet been conclusively determined, and accordingly, the actual structures of the alkaloids may be the mirror images of those given in this section.

The starting point for the arguments is undulatine (93) = (116). In this base there are five asymmetric centres of which two are the points of attachment of the 1,2-epoxide ring. This ring must be *cis* fused to the alicyclic ring and on the same side of the latter as the hydroxyl group



(107)

HEAMANTHIDINE



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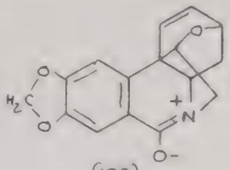

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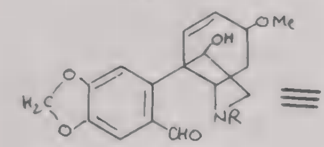

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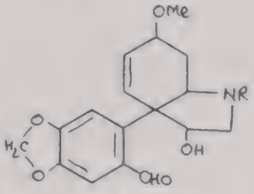

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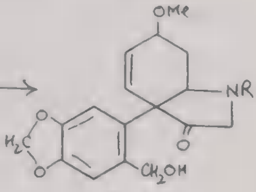

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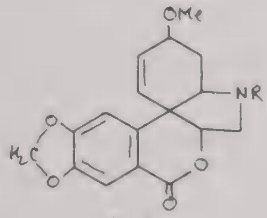

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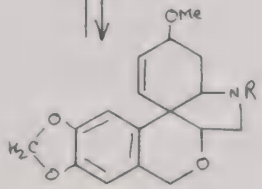

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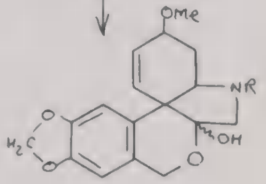

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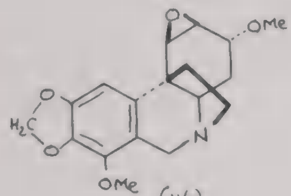
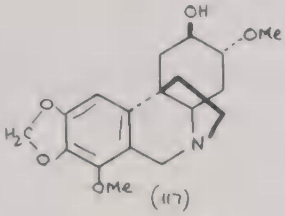
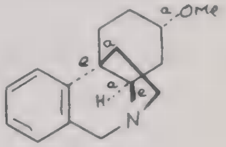


(116)

UNDULATINE



(117)



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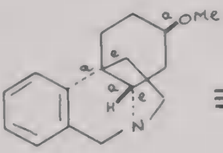

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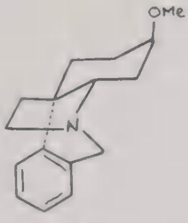

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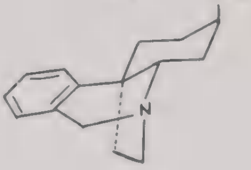

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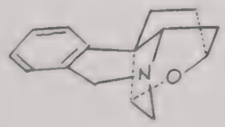

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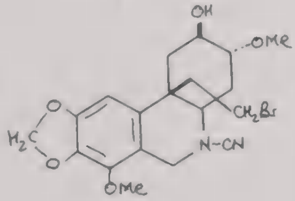
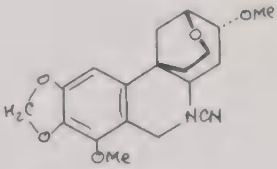


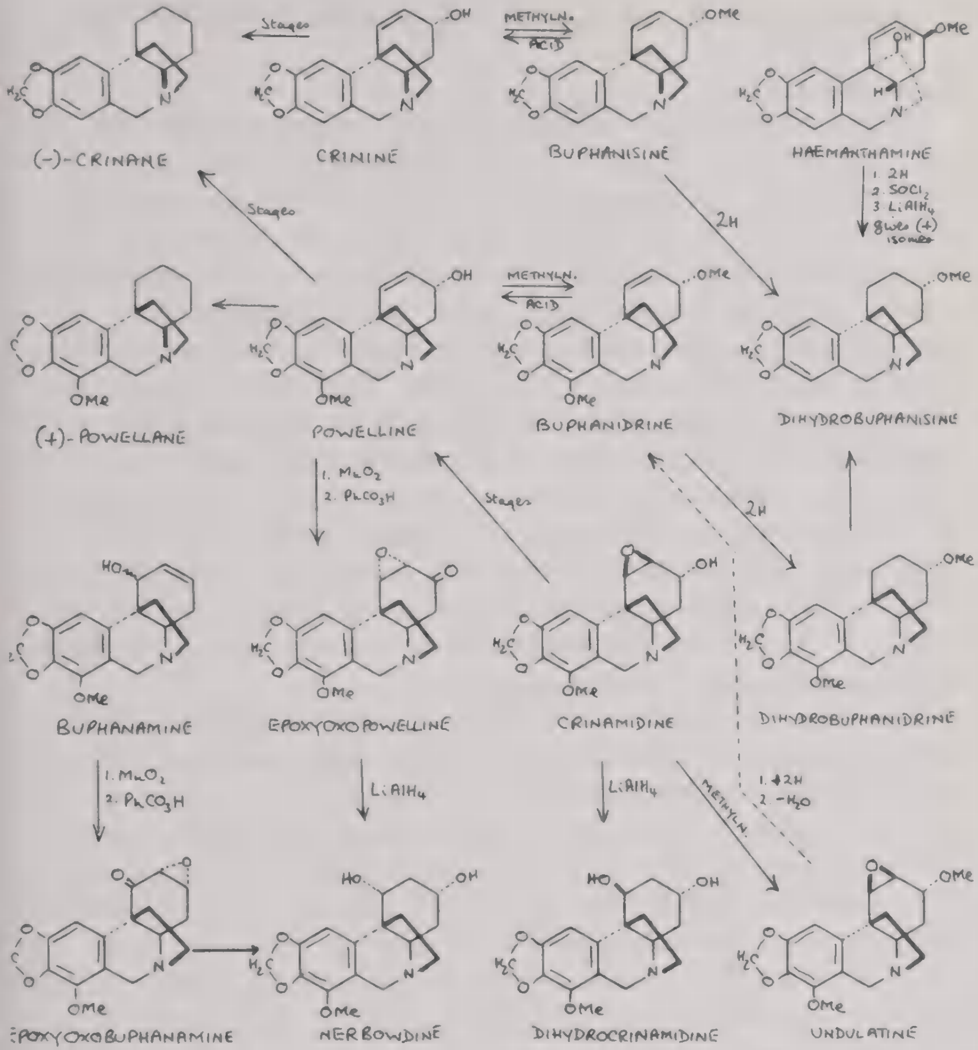
(120A)



(120B)

in dihydroundulatine (117), which is formed by reductive cleavage of the epoxide. Assuming that the hydroxylated ring in (117) is in the chair form, the methoxyl group is obviously axial, since the related ketone is very readily epimerized to a more stable form by bases. Neglecting impossible structures in which either the pyrrolidine ring or the tetrahydroisoquinoline system is fused to the hydroxylated ring of (117) through *trans* diaxial bonds, only two basic skeletons are possible namely (118) with a *cis* axial/equatorial fusion of the pyrrolidine/cyclohexane systems and (119) with a *trans* equatorial/equatorial fusion of the two. Haemanthamine and haemanthidine have been shown to belong to the same group, having been related to bases (of the enantiomorphic series) to which undulatine also has been related, and these bases must have a *cis* fusion of the hexahydroindole system, since it is only so that the ether ring in the apo-bases (104), (105) and (108) can exist, e.g. apodihydrohaemanthamine must be (120), and so the skeleton (119) can be discounted.

Treatment of dihydroundulatine with cyanogen bromide leads to a bromo-*N*-cyano compound(120A) that on treatment with base is converted into the cyclic ether (120B). The β-bromoethyl side chain at C-10b and the hydroxyl at C-2 in (120A) must therefore be *cis*, dihydroundulatine must be (117) and undulatine (116). From these facts, and the other relationships established between the alkaloids of this group, the bases must have the stereochemistry set out on the opposite page.[14, 48]


(-)-CRINANE
Stages
CRININE
METHYLN.
ACID
BUPHANISINE
HAEMANTHAMINE
1. 2H
2. SOCl₂
3. LiAlH₄
gives (+) isomer
Stages
2H
(+)-POWELLANE
POWELLINE
METHYLN.
ACID
BUPHANIDRINE
DIHYDROBUPHANISINE
1. MnO₂
2. PhCO₃H
Stages
2H
BUPHANAMINE
EPOXYOXOPOWELLINE
CRINAMIDINE
DIHYDROBUPHANIDRINE
1. MnO₂
2. PhCO₃H
LiAlH₄
LiAlH₄
METHYLN.
1. +2H
2. -H₂O
EPOXYOXOBUPHANAMINE
NERBOWDINE
DIHYDROCRINAMIDINE
UNDULATINE

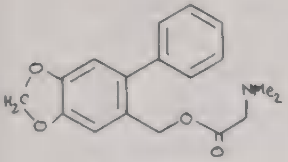
DERIVATIVES OF [2]-BENZOPYRANO-[3,4-*c*]-INDOLE

Tazettine (134)

This alkaloid is widely distributed in the *Amaryllidaceae*; it has the composition $C_{18}H_{21}O_5N$ and contains one methylenedioxy group, one methoxyl group one hydroxyl group and an *N*-methyl group and a reducible double bond. Hofmann degradation affords the base (121), the structure of which is revealed by conversion into 6-phenylpiperonyl alcohol (122) and by total synthesis.[4, 41] Accordingly, tazettine must have the part structure (123) with the methoxyl group and the double bond unplaced; the carbonyl group of the methine (121) presumably arises from the hydroxyl-bearing carbon of the alkaloid, which must either be in the oxidation state of a carbonyl group initially, or must achieve this state during degradation. When degradation is preceded by alkaline methylation, however, a number of other products are obtained in addition to the ester (121), namely the esters (124) and possibly (125), together with the corresponding alcohols, and the ether (126)[30, 49] from which the position of the methoxyl group relative to the piperonyl nucleus may be deduced.

Reduction of tazettine with lithium aluminium hydride affords a dihydro compound, tazettadiol $C_{18}H_{23}O_5N$, containing two hydroxyl groups, which may be dehydrated with formation of an ether, deoxytazettine $C_{18}H_{21}O_4N$. Hofmann degradation of the last named base gives deoxytazettine methine $C_{19}H_{23}O_4N$,[21] which is rearranged by acids to the neomethine $C_{18}H_{19}O_3N$, with loss of methanol. Further Hofmann degradation of this base gives the nitrogen-free compound (128), the structure of which is revealed by its oxidation to the lactone (129), preparable by synthesis from (130) via (131).[20, 22] Accordingly deoxytazettine neomethine may be assigned the structure (127) and deoxytazettine methine the structure (132). The alternative structure (133) for the methine is very unlikely in view of the fact that it contains a highly active hydrogen atom and would be expected to aromatize under the alkaline conditions of the Hofmann degradation, whereas rearrangement of (132) would be expected only under acid conditions.

On the basis of the above deductions tazettine may be formulated as



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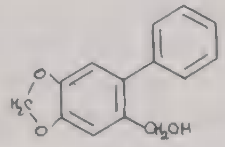

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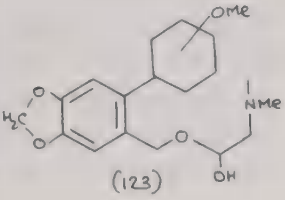

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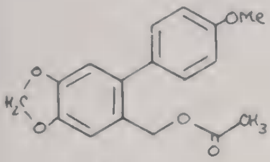

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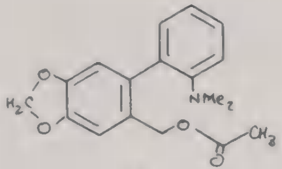

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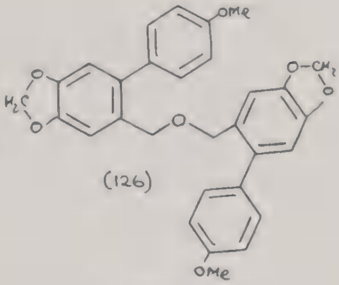

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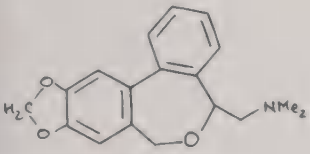

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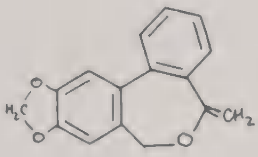

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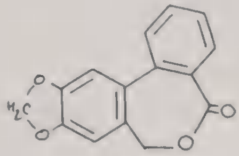
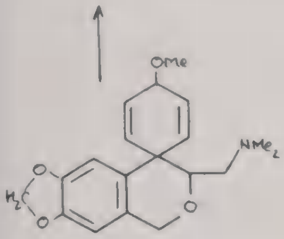
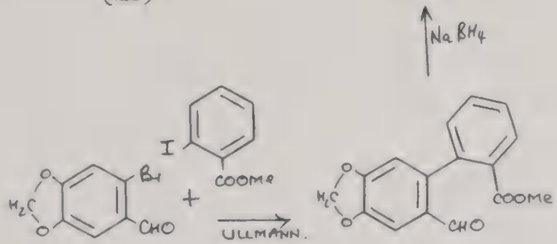


(129)

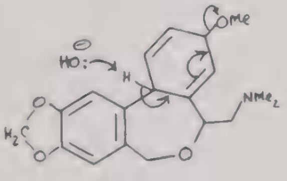


(132)



(130)

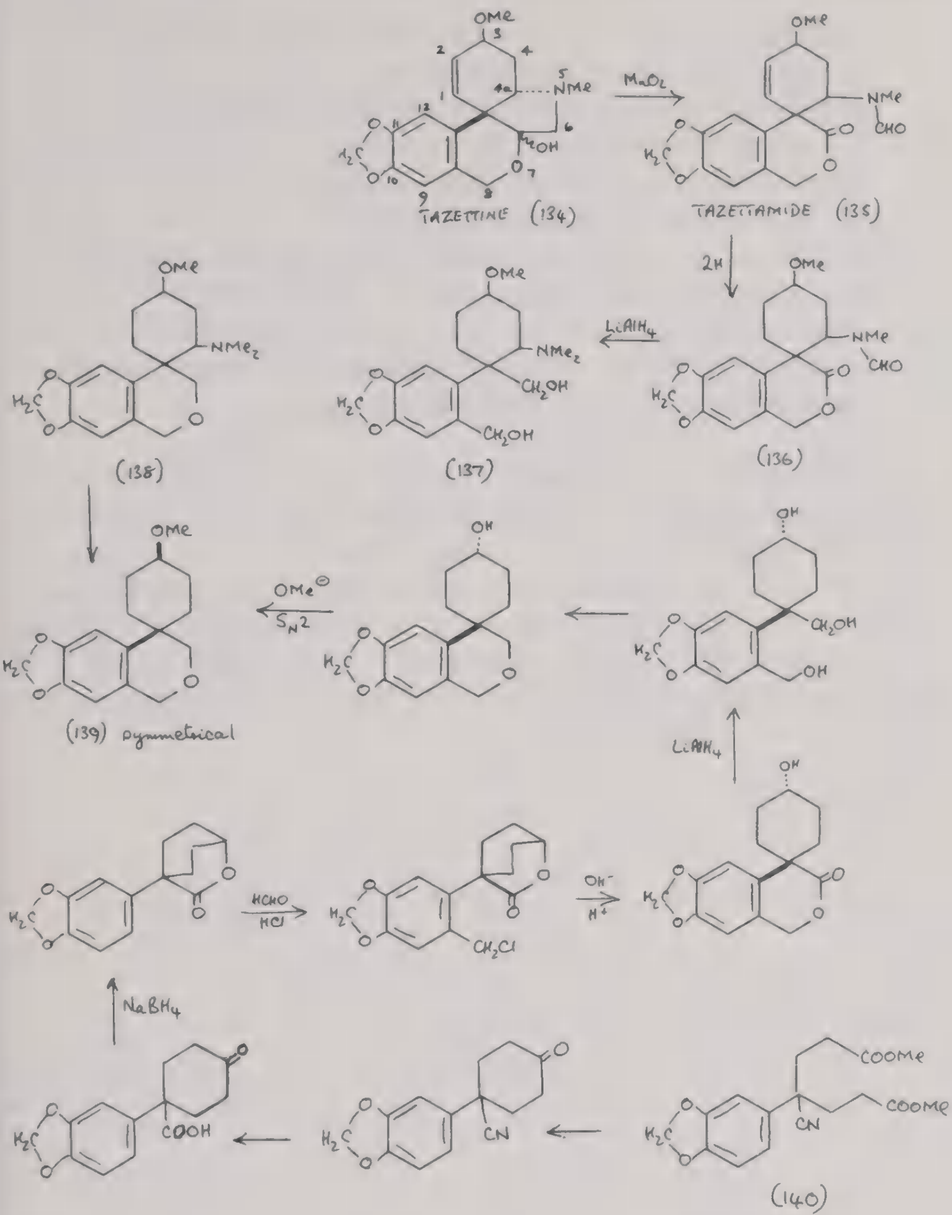
(131)



(133)

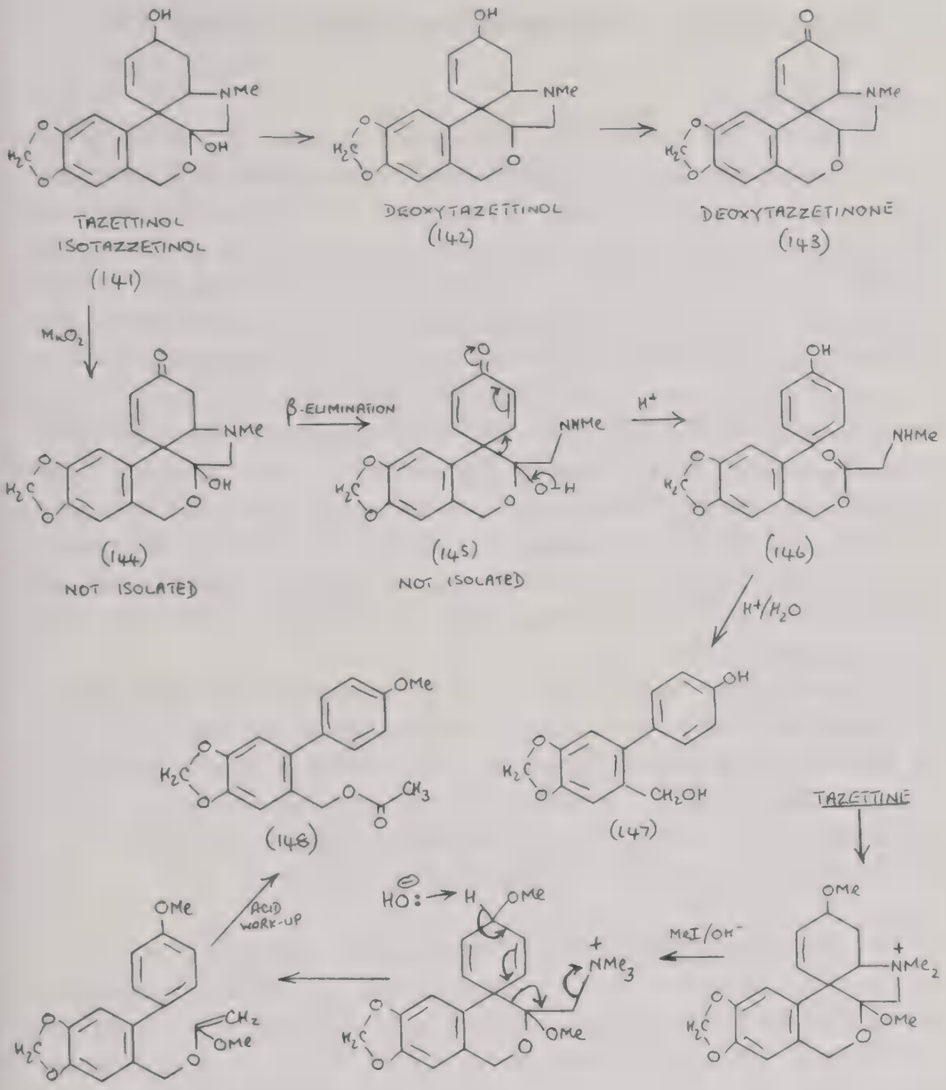
(134), and this is supported by the following evidence:

1. Oxidation of tazettine with manganese dioxide to tazettamide (135) which may be transformed into the optically inactive nitrogen-free substance (130),[17, 22] synthesized from (140) as shown;[24] this synthesis also establishes that the methoxyl group and aromatic nucleus are *cis* to each other, about the cyclohexane ring.


OMe
3
2
4
1
4a
5
NMe
12
11
6
OH
H₂C
10
9
8
7
TAZETTINE (134)
MnO₂
NMe
CHO
TAZETTAMIDE (135)
2H
(136)
LiAlH₄
NMe₂
CH₂OH
CH₂OH
(137)
(138)
OMe⊖
S_N2
(139) symmetrical
OH
CH₂OH
OH
LiAlH₄
HCHO
HCl
CH₂Cl
OH⁻
H⁺
NaBH₄
COOH
CN
COOMe
COOMe
(140)

2. Cleavage of tazettine as an allylic ether to two epimeric alcohols tazettinol and isotazettinol (141), and conversion of both these into deoxytazettinone (143) and into the alcohol (147) as shown.
3. A reasonable course for the Hofmann degradation to (124) = (148) as shown opposite. All the Hofmann degradations of tazettine derivatives may be represented generally as involving normal elimination to a primary methine, which can then suffer further base or acid-catalysed rearrangements, during isolation.
4. Tazettinol can be converted into epihaemanthamine methiodide by thionyl chloride.[27] (Epihaemanthamine is epimeric with haemanthamine at the secondary alcoholic group.)

Stereochemistry of Tazettine. The relative stereochemistry of the aromatic nucleus and the methoxyl group is fixed by the synthesis of (139) reported above. The nitrogen atom is assumed to be *trans* to the methoxyl since isotazettinol is a stronger base than tazettinol, as a result of hydrogen bonding of the nitrogen atom with the *cis* hydroxyl group. Accordingly tazettine must be (134) or its mirror image; it is represented as the former rather than the latter in a recent paper[27] but on no convincing grounds.


TAZETTINOL
ISOTAZZETINOL
(141)
DEOXYTAZETTINOL
(142)
DEOXYTAZZETINONE
(143)
MnO₂
(144)
NOT ISOLATED
β-ELIMINATION
(145)
NOT ISOLATED
H⁺
(146)
H⁺/H₂O
(147)
(148)
TAZETTINE
MeI/OH⁻
ACID WORK-UP
HO:⁻
OMe
NMe
NHMe
NMe₂
NMe₃
OH
CH₂OH
CH₃
H₂C

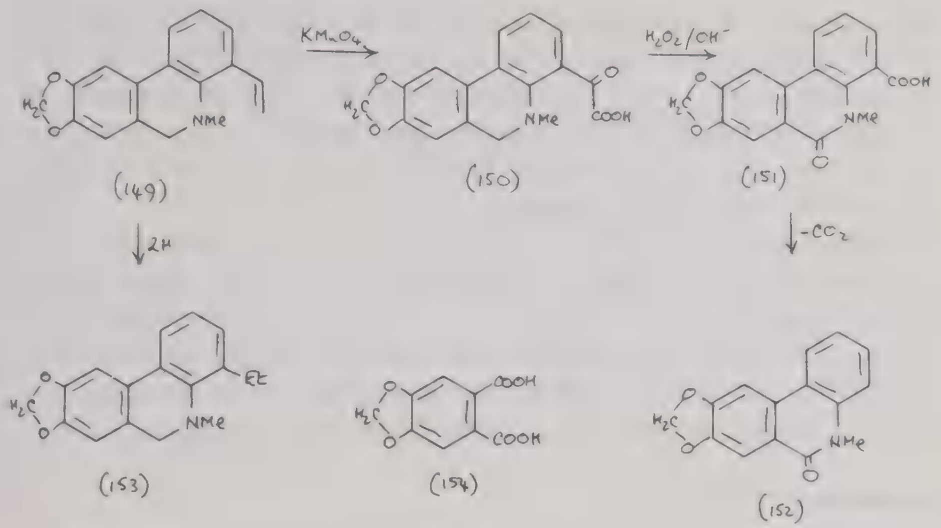
DERIVATIVES OF PYRROLO[*de*]PHENANTHRIDINE

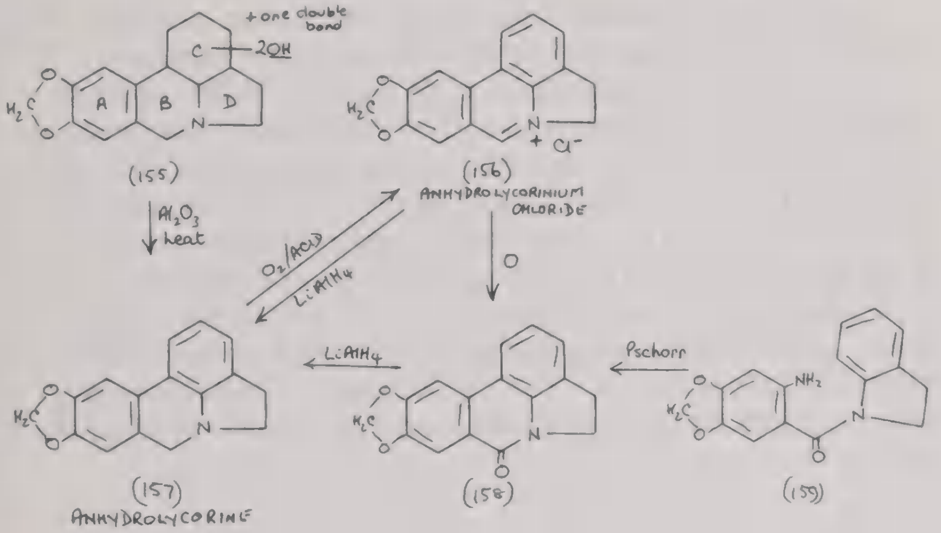
Lycorine (170)

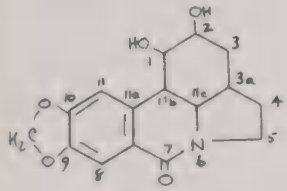
This base is one of the most widely-occurring of the whole group. It has the composition $C_{16}H_{17}O_4N$ and contains one methylenedioxy group, two alcoholic hydroxyl groups and a reducible double bond. The nitrogen atom is tertiary but is not present in an *N*-methyl group. Hofmann degradation of the alkaloid is accompanied by loss of both hydroxyl groups with aromatization and production of anhydrolycorine methine $C_{17}H_{15}O_2N$ which is identified as the vinyl compound (149) by conversion successively into (150) (151) and (152), the last of which has been synthesized,[32, 34] and also by reduction to the base (153), likewise prepared by synthesis.[25] Of the two aromatic nuclei of (149) the piperonyl nucleus must be present in lycorine since this base gives hydrastic acid (154) on oxidation, so the part structure (155) may be advanced for the alkaloid. In this the two hydroxyl groups and the double bond may be assigned to ring C to account for the very ready aromatization of this ring.

The aromatizing dehydration can be accomplished independently of Hofmann degradation by heating lycorine with alumina at 175—185°, the product being anhydrolycorine (157),[7] which in hydrochloric acid is very readily oxidized to anhydrolycorinium chloride (156), obtainable directly by the action of phosphorus oxychloride on the alkaloid.[33] Anhydrolycorine has been synthesized as shown in (159) → (158) → (157).[19]

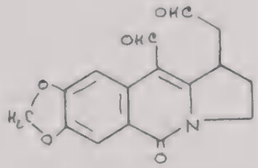
That the two hydroxyl groups of lycorine are vicinal is obvious from the ready oxidation of dihydrolycorinone, the lactam corresponding to dihydrolycorine, to a dialdehyde with lead tetraacetate[31] or periodic acid.[39] Two moles of oxidant are consumed in this reaction, the product being the carbostyril derivative (161), convertible into (162),


KMnO₄
H₂O₂/OH⁻
2H
-CO₂
H₂C
NMe
COOH
Et
(149)
(150)
(151)
(152)
(153)
(154)

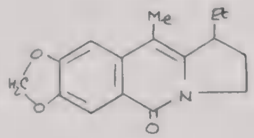

+ one double bond
2OH
A
B
C
D
Cl⁻
(155)
(156)
ANHYDROLYCORINIUM CHLORIDE
Al₂O₃ heat
O₂/ACID
LiAlH₄
O
LiAlH₄
Pschorr
NH₂
(157)
ANHYDROLYCORINE
(158)
(159)


OH
HO
3a

(160)


OHC
OHC

(161)


Me
Et

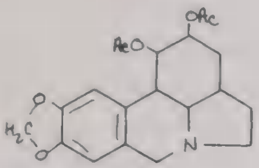
(162)

indicating that dihydrolycorinone has the structure (160).[39] The 1,2-placing of the hydroxyl groups is supported by the sequence of reactions (163) → (166), the end-product of which, being the vinylogue of an imide, is soluble in alkali.[39] Further, very mild oxidizing agents convert lycorine into the betaines (167) and (168), the structures of which are assigned on spectral grounds.[10]

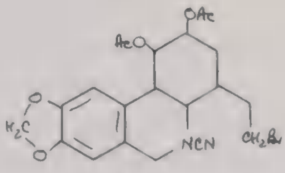
The position of the double bond follows from a study of the dissociation constants of lycorine and dihydrolycorine, which shows that it cannot be α,β to the nitrogen atom, and from the ready oxidation of monoacetyllycorine with manganese dioxide to a ketone, acetyllycorin-2-one (169) indicating that an allylic alcohol system is present in the base.[37] Lycorine may thus be assigned the complete structure (170).

Galanthine (176)

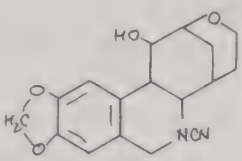
This base, from *Galanthus woronowii* and some *Narcissus* species, has the composition $C_{18}H_{23}O_4N$ and contains three methoxyl groups, one hydroxyl and a double bond. Emde degradation proceeds with aromatization and formation of (173), obtainable as shown from (171), the product of Emde degradation of lycorine.[19, 38] Mild oxidation of galanthine gives a quaternary salt (174), containing three methoxyl groups, with an ultraviolet spectrum almost identical with that of the betaine (168). Sodium /amyl alcohol reduction of the alkaloid affords the alkaloid pluviine (175) which may be oxidized to a betaine identical in UV absorption with (167). As pluviine is neither an allylic alcohol nor a substituted vinylamine it must have the double bond located as shown in (175). Galanthine is not an allylic alcohol, an enol or an enol ether, and does not contain the double bond α,β to the nitrogen or conjugated with the aromatic nucleus, and therefore may be formulated as (176).[11, 12]



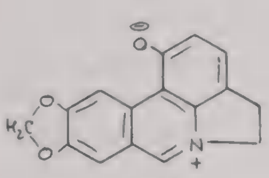
(163)



(164)



(165)



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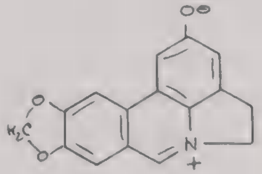
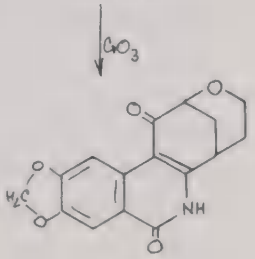
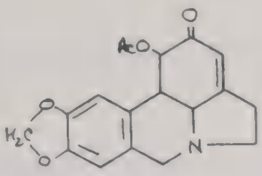


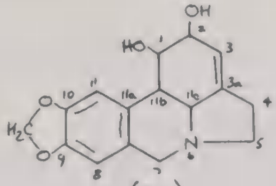
(168)



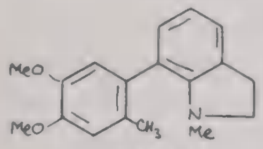
(166)



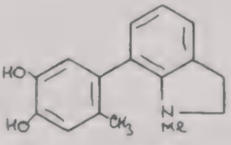
(169)



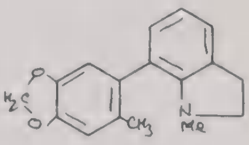
(170)



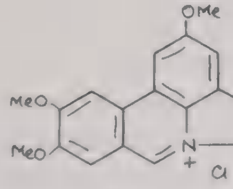
(173)



(172)



(171)



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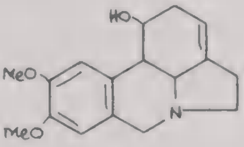
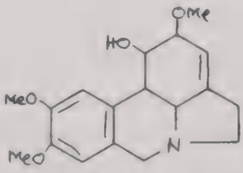


(175)



GALANTHINE
(176)

Stereochemistry

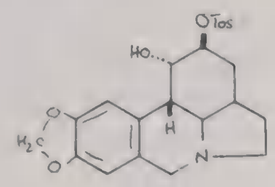
Tosylation of dihydrolycorine gives the tosyl ester (177) which can be converted into a mixture of the epoxide (178) and the methyl ether (179) by methanolic potash. The epoxide can be hydrolysed back to dihydrolycorine and reduced to α-dihydrocaranine (180) and this base and (179) can be dehydrated to the olefins (181, R=H) and (181, R=OMe) respectively. Hence the hydroxyl groups of dihydrolycorine are *trans* and diaxial, and the hydrogen at C-11*b* must be *trans* to the hydroxyl at C-1. Also the cyclization of the CH_2CH_2Br side chain of (164) with the C-2 hydroxyl group indicates that these groups are *cis* (and therefore both axial) and therefore the C-11*a*:N bond must be equatorial for a *trans* diaxial fusion of rings C and D is impossible. Thus lycorine must be (182) or its mirror image;[40] the mirror image structure is ruled out by a consideration of molecular rotation differences of lycorine and its C-3 epimer.[36]

DERIVATIVES OF [2]BENZOPYRANO[3,4-*g*]INDOLE

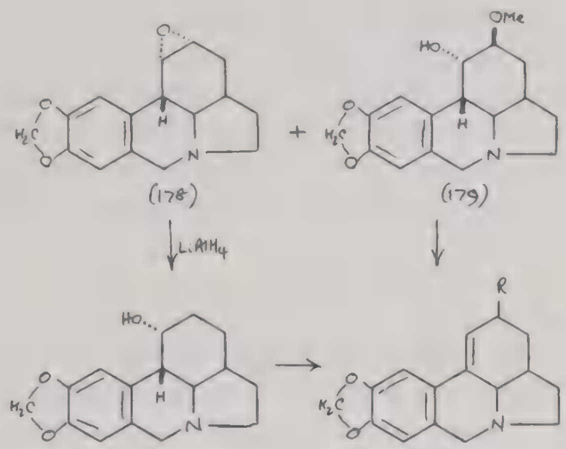
Lycorenine (194)

Lycorenine, an alkaloid from various *Lycoris* and *Narcissus* species has the composition $C_{18}H_{23}O_4N$, and contains one *N*-methyl group, two methoxyl groups, two non-phenolic hydroxyl groups and a reducible double bond. Reduction of the base catalytically proceeds with concomitant hydrogenolytic loss of a hydroxyl group to give dihydrodeoxylycorenine and electrolytic reduction gives deoxylycorenine itself. Chromic acid oxidation of the base affords homolycorine, a naturally occurring base that contains a δ-lactone system. These reactions are best explained on the basis of the part structure (183), in which the alkaloid is represented as the hemiacetal of an aromatic aldehyde[3, 5, 18, 26,] and this is further supported by the lithium aluminium hydride reduction of lycorenine and homolycorine to the same diol, which may be dehydrated by dilute acids to deoxylycorenine.

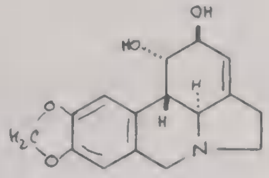
Hofmann degradation of lycorenine affords a methine base with loss of water and aromatization, and further degradation of the methine yields a vinyl compound giving on ozonolysis a dialdehyde that may be oxidized to the diphenyl derivative (186), the structure of which is obvious from its synthesis as shown.[29] From this it may be deduced that the vinyl compound is (185) and the methine base is (184). The



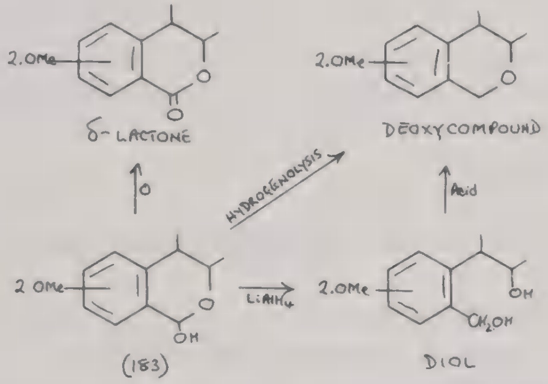
(177)



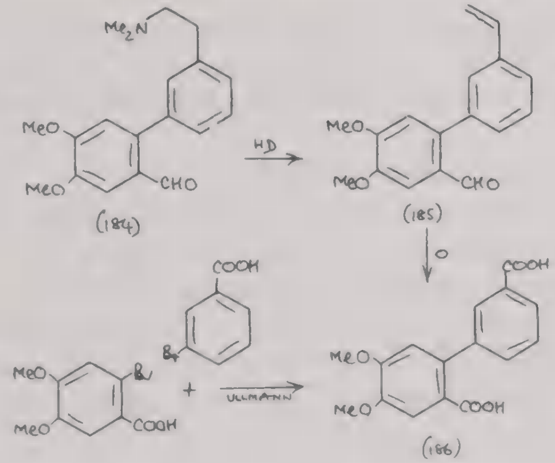
(178) (179) (180) (181)



(182)



(183)



(184) (185) (186)

point of attachment of the nitrogen atom in the original alkaloid is demonstrated by Wolff–Kishner reduction of lycorenine to a base that must have the structure (187), since on aromatization it yields the pyrroles (188) and (189), the last of which is also preparable from lycorine (190) via (191) and (192).[46] Lycorenine must therefore have the structure (193) containing one so far unplaced double bond.

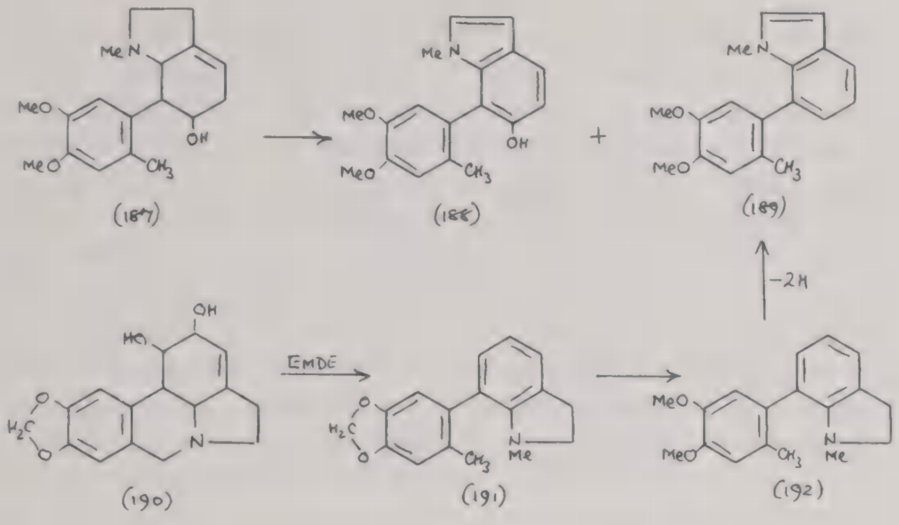
Catalytic reduction of lycorenine affords two diastereoisomeric dihydro-deoxy compounds indicating that a new asymmetric centre is created by the saturation of the double bond, and since the spectra and properties of the alkaloid show that this double bond is not α,β to the nitrogen or conjugated with the aromatic nucleus, and since lycorenine is not an enol ether, the alkaloid must have the structure (194) or the isomeric structure with a 3,3a double bond. Of these two possibilities (194) is shown to be correct since tetrahydrohomolycorine (196), the product of lithium aluminium hydride reduction of lycorenine and homolycorine, gives, with *p*-toluenesulphonyl chloride and pyridine, the quaternary salt (197), the related chloride of which on dry distillation affords pluviine (198). Since the stereochemistry of pluviine is as shown in (198) that of lycorenine must be as in (194) and of homolycorine as (195).[27]

DERIVATIVES OF 5,11-METHANOMORPHANTHRIDINE

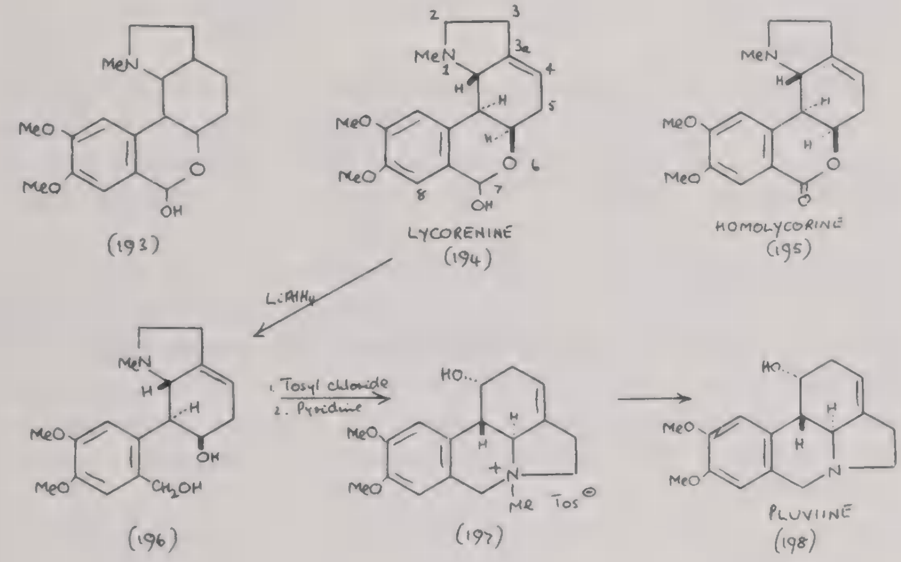
A group of alkaloids derived from a new ring system has recently been discovered and is represented by montanine, coccinine, and manthine and probably also by manthidine and brunsvigine. These bases are found in *Haemanthus coccineus*, *H. amylloides*, *H. montanus* and *H. tigrinus*. They may arise from precursors of the haemanthidine type, from which they have been prepared in the laboratory.

Montanine (222) and Coccinine (223)

These two alkaloids are diastereoisomers of composition $C_{17}H_{19}O_4N$, and contain a methylenedioxy group, a methoxyl group, one alcoholic hydroxyl group and one reducible double bond. The spectral properties, the failure of reactions characteristic of the lycorine group, and the absence of *N*-methyl and cyclic ether groups, clearly shows that these bases do not belong to any of the groups of alkaloids discussed in the previous pages.



(187) (188) (189) (190) (191) (192)



(193)

LYCORENINE (194)

HOMOLYCORINE (195)

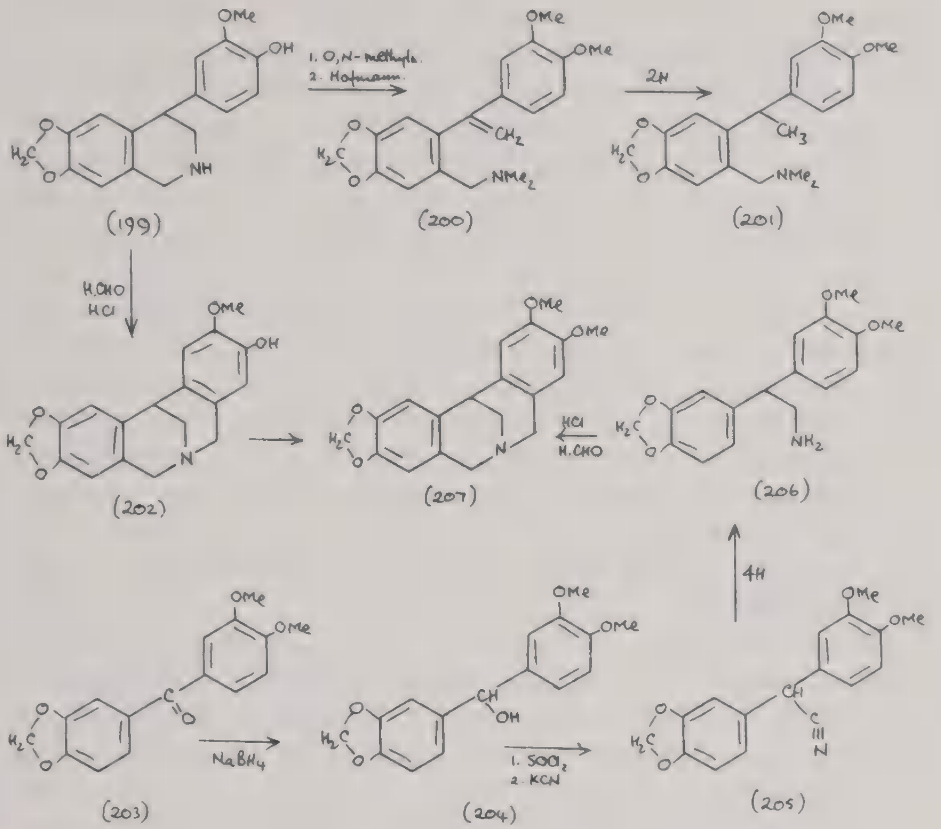
(196) (197)

PLUVIINE (198)

Oppenauer oxidation of the two bases affords the same product, dehydrococcinine, $C_{17}H_{17}O_4N$, which is a secondary aminophenol containing a new aromatic nucleus not in conjugation with that originally present in the parent bases. Aromatization is not uncommon in the *Amaryllidaceae* alkaloids but is usually accompanied by loss of optical activity, whereas dehydrococcinine is still optically active. Methylation of the phenolic group of this new base, followed by Hofmann degradation, leads to an optically inactive methine base having the ultraviolet absorption of a 1,1-diarylethylene. Reduction of this last base gives a dihydromethine showing ultraviolet absorption characteristic of isolated aromatic nuclei. These results are compatible with the structure (199) for dehydrococcinine, (200) for the methyl ether methine and (201) for the dihydromethine, and this structure for dihydrococcinine (or the isomeric structure with the positions of the methoxyl and hydroxyl groups interchanged) is confirmed by condensation of the base with formaldehyde to give (202), the methyl ether of which (207) has been synthesized by the route (203) → (207).[23]

The structures of the two parent alkaloids and the precise structure of dehydrococcinine follow from a consideration of the course of the Oppenauer oxidation leading to the latter. The two alkaloids must be diastereoisomers of structure (208), Oppenauer oxidation of which would give the β-aminoketone (209) in which β-elimination would give the ketonic form (210) of the phenol (199). Reversal of the positions of methoxyl and hydroxyl in (208) would give a base in which such an elimination reaction would not be expected. The double bond in the alkaloids must be placed as in (208), since neither is an enol or an enol ether or a substituted vinylamine. Indeed the bases are allylamines and hydrogenolysis with production of secondary bases always accompanies hydrogenation.[23]

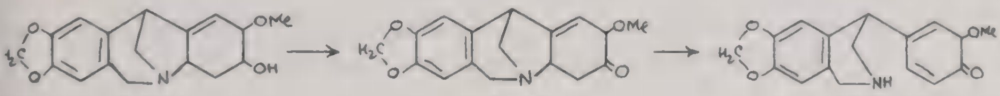
Correlation of these bases with the haemanthamine series has been



(199) (200) (201)

(202) (207) (206)

(203) (204) (205)

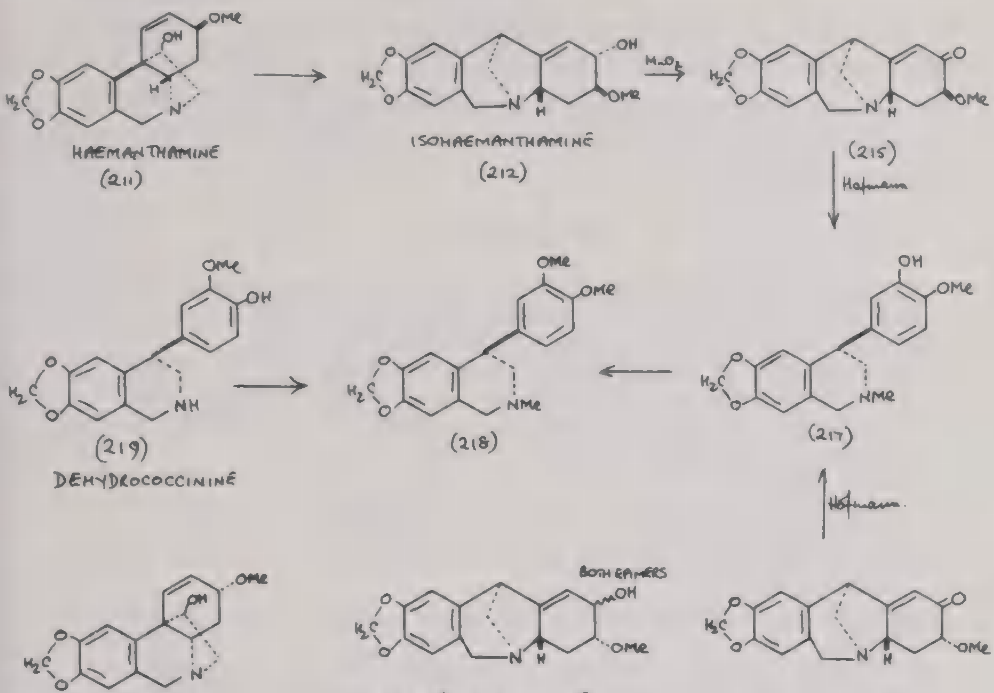


(208) (209) (210)

accomplished in the following way. Hydrolysis of the methanesulphonyl ester of haemanthamine (211) with aqueous alkali affords a base, isohaemanthamine, isomeric with haemanthamine, montanine and coccinine, to which the structure (212) may be assigned. Two more bases of the same composition result from the hydrolysis of *O*-methanesulphonyl crinamine (213) and these are diastereoisomers of structure (214) differing only at the secondary alcoholic group, since both bases give the same ketone on oxidation. That these bases are allylic alcohols is demonstrated by oxidation with manganese dioxide to isomeric α,β-unsaturated ketones, oxoisohaemanthamine (215) and oxoisocrinamine (216), differing only in the disposition of the methoxyl group *alpha* to the carbonyl, as (215) can be epimerized to (216) by alkali, in which these bases are apparently much more stable than the isomeric (209) postulated as an intermediate in the Oppenauer oxidation of coccinine. Hofmann degradation of (215) and (216) gives the same phenolic base (217) the methyl ether of which (218) is identical with material prepared from dehydrococcinine (219).

The stereochemistry of (215), (216), (217) and hence of dehydrococcinine and the carbon–nitrogen skeleton of coccinine and montanine follows from the known stereochemistry of haemanthamine (211) and crinamine (213). The methanesulphonyl group of the mesyl ester of haemanthamine is well situated for nucleophilic displacement by the aryl group in the *trans* antiparallel position. The rearrangement, represented in formulae (219) → (220) is completed by attack of base at C-2 and migration of the double bond; using aqueous alkali the introduced group OR is hydroxyl but with methanolic sodium methoxide it is methoxyl.[23]

By spectral studies the configuration of the hydroxyl group in isohaemanthamine is believed to be as shown in (212) and *O*-methylation of the base gives the alkaloid manthine, which must accordingly be (221), and as this base is also the methyl ether of montanine, montanine must be (222). The methylation of α- and β-isocrinamine (214) affords two methyl ethers neither of which is identical with coccinine, which must therefore be epimeric with montanine at the —CH(OMe)— and not the —CH(OH)— group. This is confirmed by the sodium borohydride reduction of (125) to epi-isohaemanthamine and the *O*-methylation of



HAEMANTHAMINE (211)

ISOHAEMANTHAMINE (212)

(215)

(219) DEHYDROCOCCININE

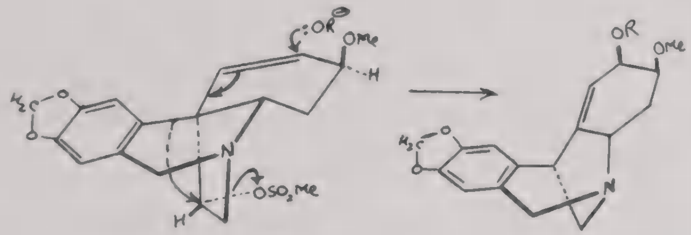
(218)

(217)

CRINAMINE (213)

α- AND β-ISOCRINAMINE (214)

(216)



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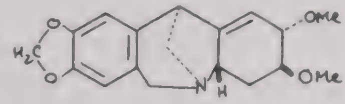
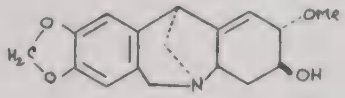
(220)



MANTHINE (221)



MONTANINE (222)

this to coccinine methyl ether; coccinine thus has the structure (223).[23]

Of the other alkaloids of this group it is very probable that brunsvigine is the dihydroxy analogue of montanine (222, OMe = OH) and that manthidine is (224), which on methylation should give *O*-methyl-β-isocrinamine.[23]

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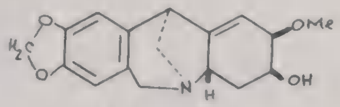
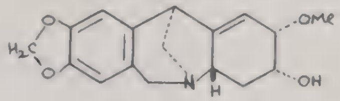


COCCININE
(223)



MANTHIDINE ?
(224)

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CHAPTER 5

STEROID ALKALOIDS

Alkaloids based on the steroid nucleus are not very widely distributed, being restricted to plants of the *Holarrhena*, *Solanum* and *Veratrum* species. Among the bases there is relatively little variation in structural type, but the following sub-groups may be distinguished.

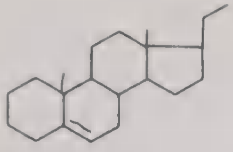
1. Derivatives of Δ^5-pregnene, e.g. conessine (1) and holarrhimine (2), present mainly as free bases or their salts in plants of the *Holarrhena* species.
2. Derivatives of solanidane [e.g. solanidine (3)] and the closely related skeleton (4), [e.g. tomatidine (5)] occurring naturally as glycosides in *Solanum*, *Lycopersicum* and *Veratrum* species.
3. Derivatives of the veratramine (6) and jervine (7) skeletons or of the related hexacyclic structure, e.g. veracevine (8). The relationship of the veracevine and jervine skeletons is immediately obvious if the latter is drawn as in (7a). These bases exist as glycosides or, more commonly, as esters in plants of the *Veratrum* species.

It is convenient to deal with the alkaloids separately on the basis of these divisions. Extended surveys of the bases have been made elsewhere.[40, 57, 58.]

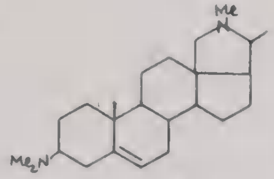
DERIVATIVES OF Δ^5-PREGNENE

Conessine (17)

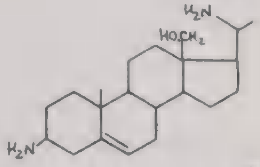
This alkaloid, from *Holarrhena antidysenterica* Wall. and *H. africana* DC., has the composition $C_{24}H_{40}N_2$ and contains one reducible double bond and three *N*-methyl groups, and must therefore contain the group —NMe_2. The presence of such a group is confirmed by the elimination of trimethylamine in the first Hofmann degradation, which gives



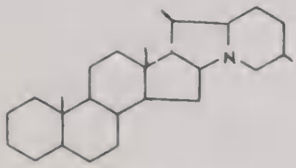
Δ⁵- PREGNENE



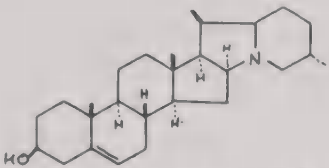
CONESSINE (1)



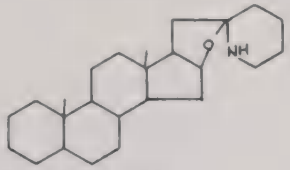
HOLARRHIMINE (2)



SOLANIDANE



SOLANIDINE (3)



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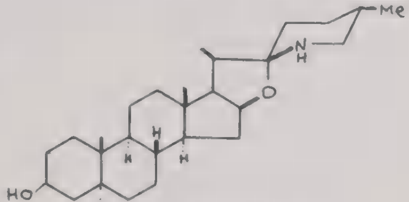
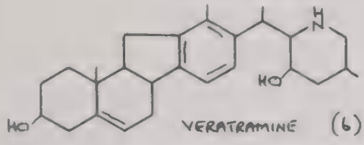
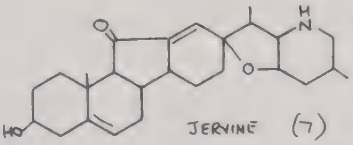


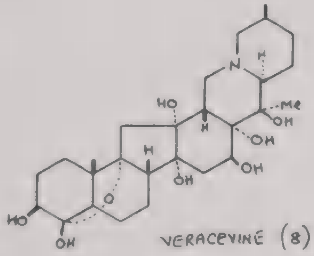
TOMATIDINE (5)



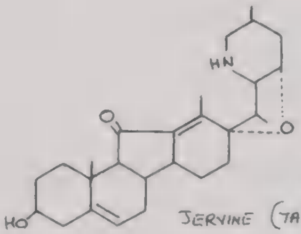
VERATRAMINE (6)



JERVINE (7)



VERACEVINE (8)



JERVINE (7A)

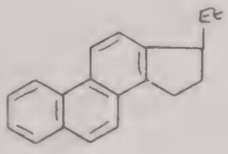
apoconessine; this is still a base, indicating that the second nitrogen is present as an NMe group in a ring.[44, 76] After allowance is made for the double bond the composition of the alkaloid implies that it is pentacyclic. Dry distillation of the dihydroiodide and dehydrogenation of the product (conessene $C_{21}H_{30}$) gives γ-ethyl-1,2-cyclopentenophenanthrene (9), indicating a probable relationship with the steroids, and this is confirmed by Emde degradation of apoconessine (the Hofmann degradation product) to pregna-3,5,20-triene (10), prepared also by the dehydration of 3β-hydroxypregna-5,20-diene (11).[26] This degradation establishes the carbon skeleton of the alkaloid, and the position of the NMe_2 group and of the double bond is demonstrated by the following reactions. Treatment of conessine with cyanogen bromide and subsequent hydrolysis of the *N*-cyano compound gives a secondary base, identical with the alkaloid isoconessimine, by the process:

$$Me_2N— \rightarrow Me(CN)N— \rightarrow MeHN—$$

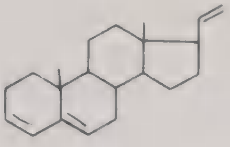
and *N*-acetylisoconessimine on Hofmann degradation followed by Emde reduction, gives the acetylated base (12), synthesized as shown from 3β-hydroxyprena-5,20-diene (11).[27]

The vinyl group of the nitrogen-free substance (10), which is also present in (12) but not in conessine, must arise during the Hofmann degradation, and the cyclic nitrogen must be attached to one of the carbon atoms of this group in the parent alkaloid. This point of attachment cannot be the terminal carbon atom since the nitrogen ring of conessimethine (14), the product of controlled Hofmann degradation of conessine, can be recyclized to give heteroconessine, a diastereoisomer of conessine, which differs from the natural base only at the carbon joined directly to nitrogen, since both afford the same methine base (14)[21, 25] and give the same dehydro base on dehydrogenation.[22] The second point of attachment of the nitrogen atom must be the carbon of the angular substituent between rings C and D, since degradation of hexahydroapoconessine (15) leads to the primary base (16),[8] which by means of the Sommelet reaction can be converted into an *aldehyde*, and this can only be 18-oxo-5α-pregnane (17) because on steric grounds the nitrogen cannot be attached to the angular substituent at C-10.[51]

Conessine may thus be assigned the complete structure (18), in which the stereochemistry at positions 3, 8, 9, 10, 13, 14, and 17 is fixed by the conversion of the base into pregna-3,5,20-triene (10) and of



(9)



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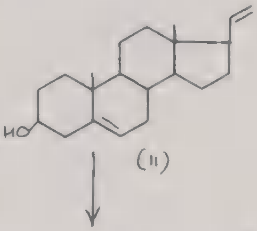

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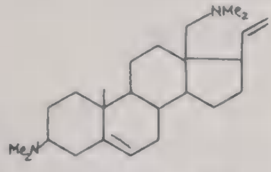
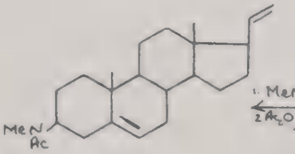


CONESSIMETHINE
(14)



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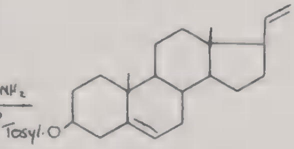

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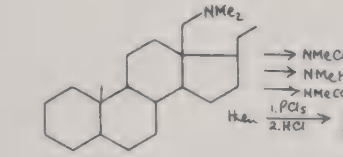

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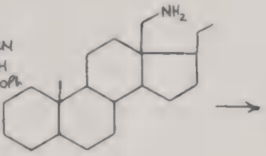

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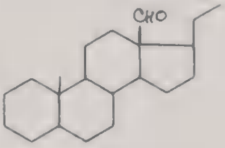


(17)

3α-hydroxypregna-5,20-diene (11) into the acetylated base (12), and that at C-20 rests on conformational analysis.

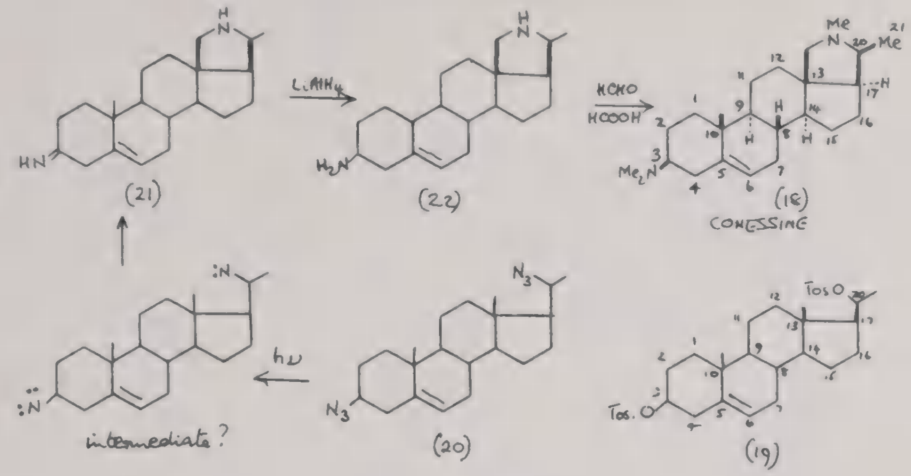
The structure (18) has been amply confirmed by the following synthesis:

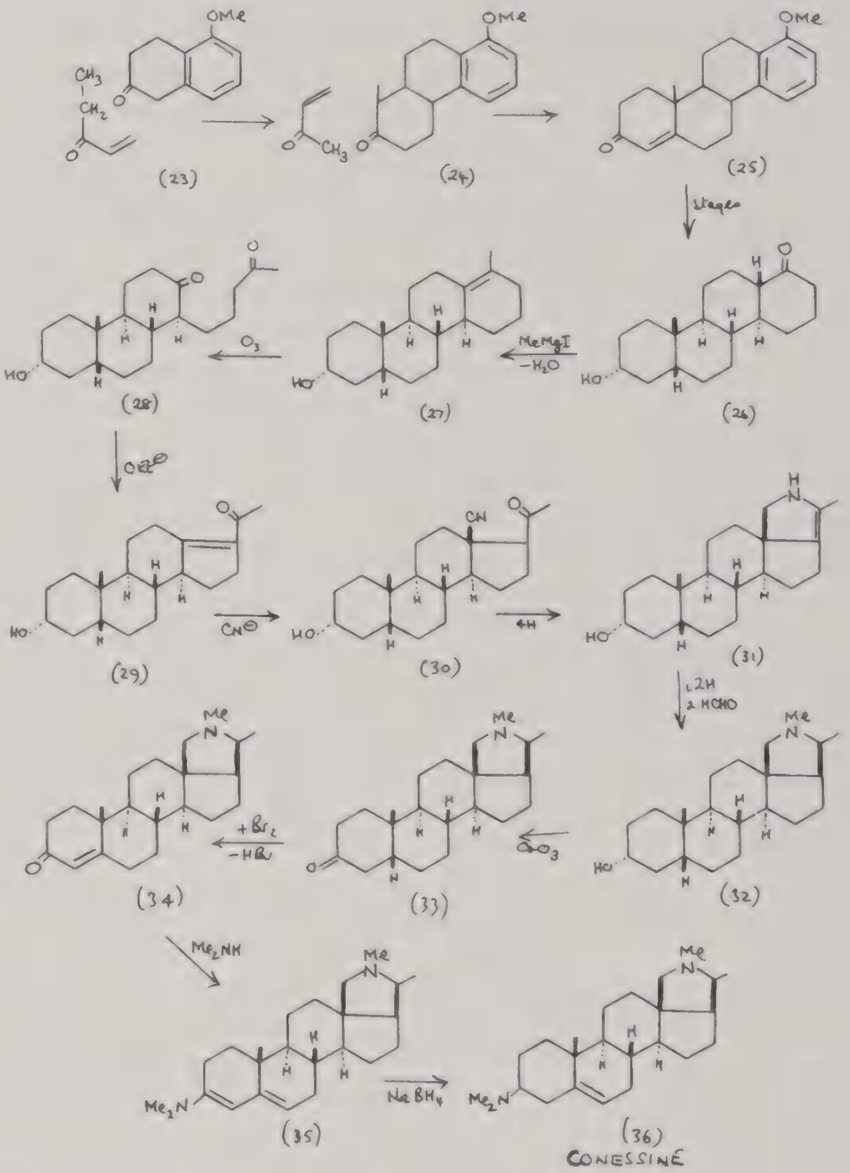
(a) From pregn-5-ene-3β,20β-diol ditoluenesulphonate (19) by the route (19) → (22) → (18) making use of a new photochemical reaction of azides.[5]

(b) Total synthesis of (±)-conessine by the routes (23) → (36)[43, 52] and (37) → (57).[42, 77]

Of the other alkaloids of this group conharrimine has the structure (18) with $—NH_2$ and —NH— groups, conimine has —NHMe and —NH—, conamine $—NH_2$ and —NMe—, conessimine $—NMe_2$ and —NH— and isoconessimine —NHMe and —NMe— groups. 3-Epiheteroconessine, differing from conessine in stereochemistry at positions 3 and 20, has also been found naturally.[79]

Conkuressine, another of the alkaloids from the bark of *Holarrhena antidysenterica*, is isomeric with conessine but is believed to contain a 7,8 double bond, the position of which is deduced from ozonolysis studies and an examination of the spectra of the base and its ozonolysis and oxidation products.[79]


HN
(21)
LiAlH4
H2N
(22)
HCHO
HCOOH
Me
N
Me
Me2N
(18)
CONESSINE
:N
:N
intermediate?
hν
N3
N3
(20)
TosO
Tos.O
(19)


OMe
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(23)
CH_3
(24)
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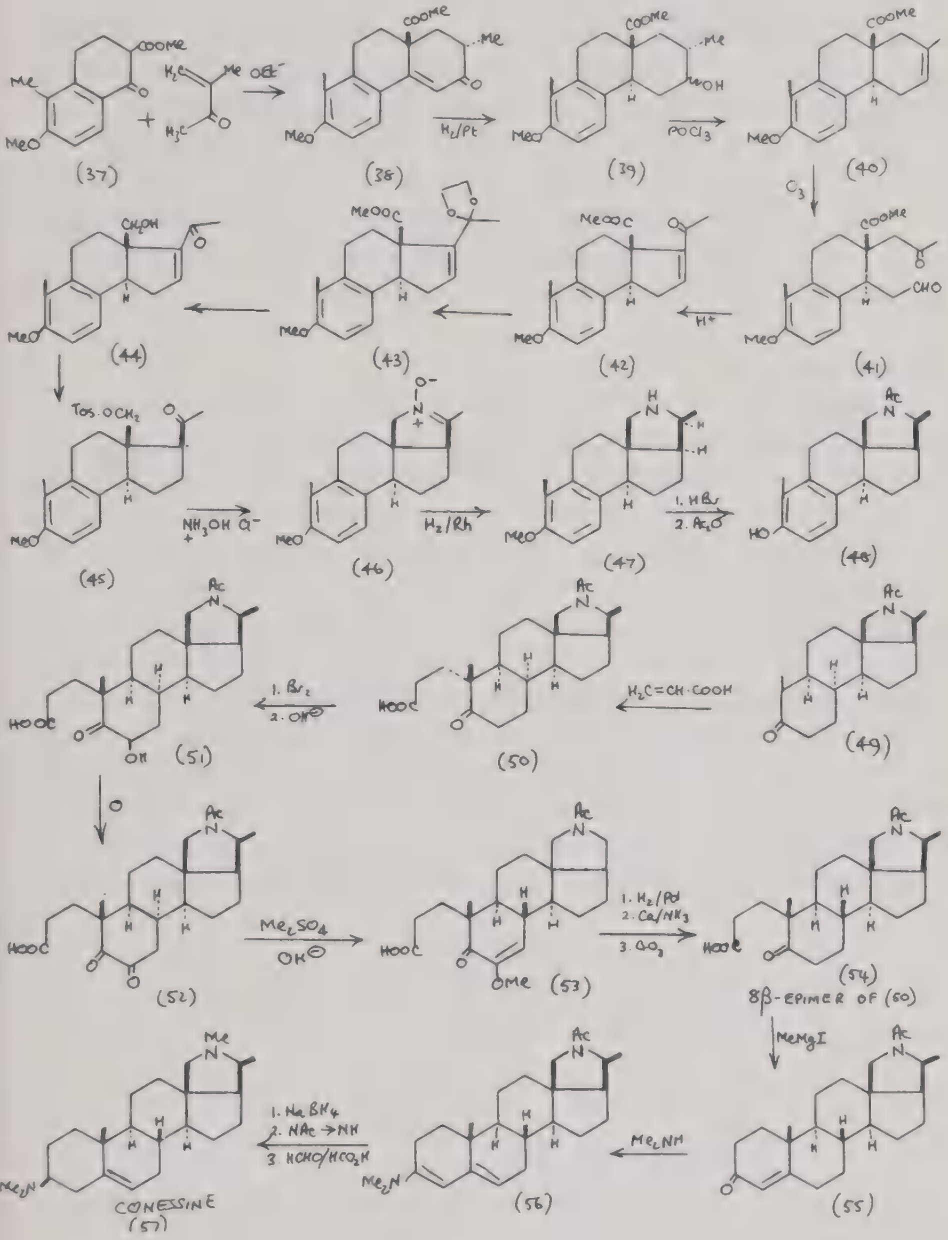
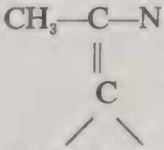
stages
(26)
MeMgI
$-H_2O$
(27)
O_3
(28)
$OH^{\ominus}$
(29)
$CN^{\ominus}$
CN
(30)
+H
(31)
1. 2H
2. HCHO
Me
(32)
CrO_3
(33)
$+Br_2$
$-HBr$
(34)
Me_2NH
Me_2N
(35)
$NaBH_4$
(36)
CONESSINE
HO
H

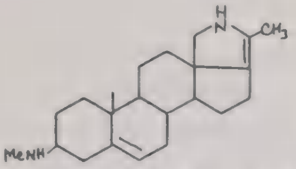

(37)
OEt⁻
(38)
H₂/Pt
(39)
POCl₃
(40)
O₃
(41)
H⁺
(42)
(43)
(44)
Tos.OCH₂
(45)
NH₃OH Cl⁻
(46)
H₂/Rh
(47)
1. HBr
2. Ac₂O
(48)
(49)
H₂C=CH·COOH
(50)
1. Br₂
2. OH⁻
(51)
O
(52)
Me₂SO₄
OH⁻
(53)
1. H₂/Pd
2. Ca/NH₃
3. O₃
(54)
8β-EPIMER OF (50)
MeMgI
(55)
Me₂NH
(56)
1. NaBH₄
2. NAc → NH
3. HCHO/HCO₂H
CONESSINE
(57)

Conessidine (58)

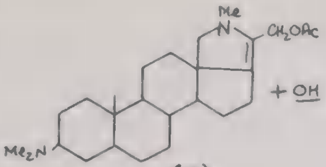
This base, isolated from the same source as conessine, has the composition of $C_{22}H_{34}N_2$ and contains one *N*-methyl group and two reducible double bonds, one of which is readily saturated to give conimine (see above). The base on ozonolysis gives a mixture that on decomposition with alkali affords acetic acid indicating that the group  $\mathrm{CH_3{-}\underset{\underset{/\ \backslash}{\overset{\|}{C}}}{C}{-}N}$ is present in the alkaloid which must accordingly be formulated as (58).[80] This position of the second double bond is supported by anology with kurcholessine (59) which on ozonolysis affords a base having the properties and spectra of an α-acetoxycarbonyl compound.[79]

Holarrhimine (72)

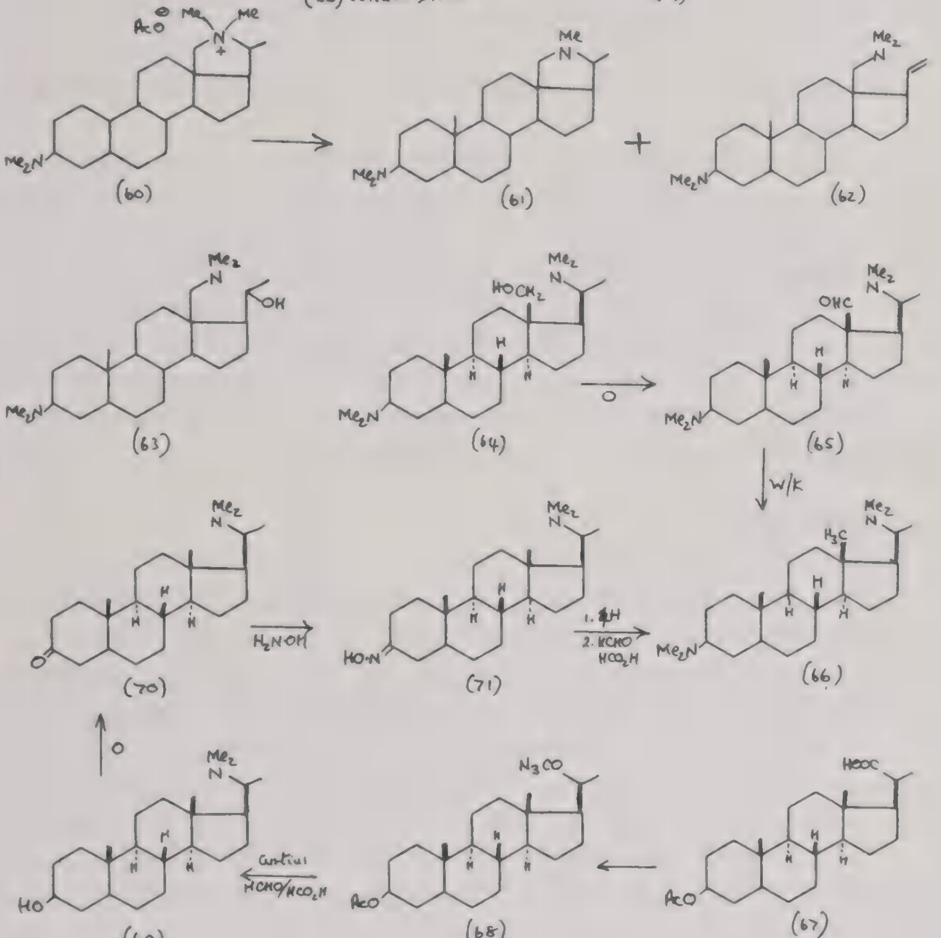
Holarrhimine has the composition $C_{21}H_{38}ON_2$ and contains one reducible double bond, two primary amino groups and one alcoholic hydroxyl. The *N*-tetramethyldihydro compound on treatment with thionyl chloride affords a quaternary salt (60) that may be converted, through pyrolysis of the acetate into dihydroconessine (61) and dihydroconessimethine (60).[48, 49] Accordingly, *N*-tetramethyldihydroholarrhimine must have the structure (63) or (64), and the former can be discounted since this base can be oxidized to an *aldehyde* (65) further oxidizable to an acid and reducible (Wolff–Kishner) to 3β,20α-bisdimethylamino-5α-pregnane (66)[15] which in turn is accessible by partial synthesis from 3β-acetoxybisnorallocholanic acid (67) via the intermediate (68) → (71) as shown.[14] Thus holarrhimine may be assigned the structure (72) in which the double bond is place at C-5 : C-6 by analogy with most of the other bases derived from *Holarrhena* species.

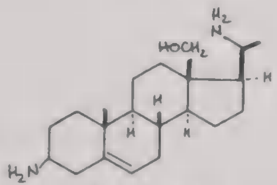


(58) CONESSIDINE



(59)





HOLARRHIMINE

(72)

Latifoline (73)

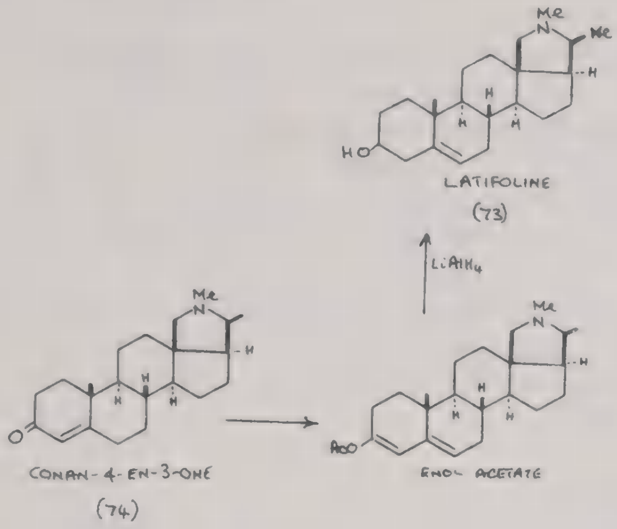
The alkaloid latifoline, from *Funtumia latifolia* Stapf. has the composition $C_{22}H_{33}ON$ and contains one alcoholic hydroxy group, one *N*-methyl group and a reducible double bond, and has been shown to have the structure (73) by partial synthesis by the lithium aluminium hydride reduction of the enol acetate of conan-4-en-3-one(74).[38]

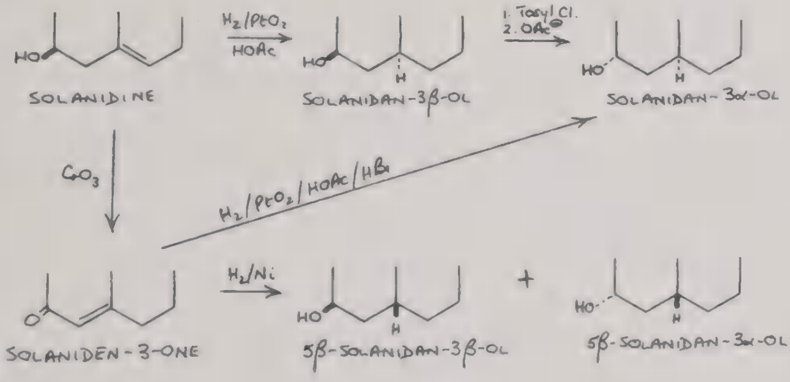
DERIVATIVES OF SOLANIDANE AND RELATED BASES

The alkaloids of this sub-group occur in many *Solanum* species, including *S. nigrum*, *S. tuberosum* (potato) and *S. lycopersicum* (tomato), and are responsible for the immunity to attack by insects of certain plants of these species. In the plants the alkaloids present generally are glycosides of a wide variety of sugars and a relatively small group of steroidal bases; a few of these simpler bases have been isolated directly from the plants but there is no real certainty that they occur in this way naturally. Hydrolysis of the glycosides readily gives the free alkamines and only these will be discussed here.

Solanidine (82)

This base, obtained by the hydrolysis of the naturally occurring alkaloids, α, β and γ-solanine, α, β and γ-chaconine and solacauline, has the composition $C_{27}H_{43}ON$ and contains an alcoholic hydroxyl group, a reducible double bond (and must thus be hexacyclic), a tertiary nitrogen that does not bear a methyl group and four *C*-methyl groups. It is resistant to Hofmann degradation and degradation with cyanogen bromide. The alcoholic group must be secondary since oxidation over hot copper powder converts solandine into a ketone, and, as this reacts twice with benzaldehyde and with amyl nitrite it must contain the system $—CH_2—CO—CH_2—$.[68] Oxidation by the Oppenauer process, however, affords an α,β-unsaturated ketone which on reduction gives a mixture of two α,β-unsaturated alcohols neither of which is identical with solanidine. From this it may be concluded that the alkaloid is a β,γ-unsaturated alcohol and the existence of four different saturated alcohols, arising as shown opposite.[6, 19, 60, 63] This behaviour, and the fact that several of the alcohols in this group give precipitates with digitonin, which is a typical reaction of 3β-hydroxysteroids, led to an early suggestion that solandine contains the steroid skeleton.

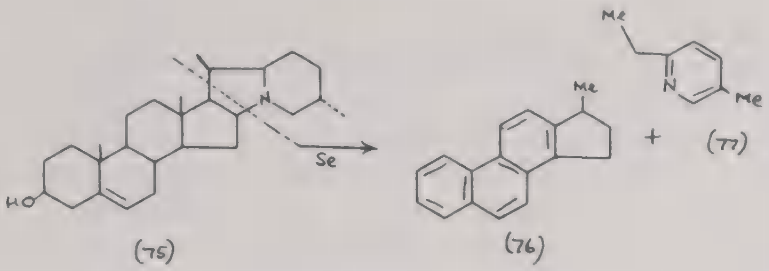

Me
N
Me
H
H
H
H
HO
LATIFOLINE
(73)
LiAlH₄
Me
N
H
H
H
H
O
CONAN-4-EN-3-ONE
(74)
Me
N
H
H
H
H
AcO
ENOL ACETATE


HO
SOLANIDINE
H₂/PtO₂
HOAc
HO
H
SOLANIDAN-3β-OL
1. Tosyl Cl.
2. OAc⊖
HO
H
SOLANIDAN-3α-OL
CrO₃
H₂/PtO₂/HOAc/HBr
O
SOLANIDEN-3-ONE
H₂/Ni
HO
H
5β-SOLANIDAN-3β-OL
+
HO
H
5β-SOLANIDAN-3α-OL

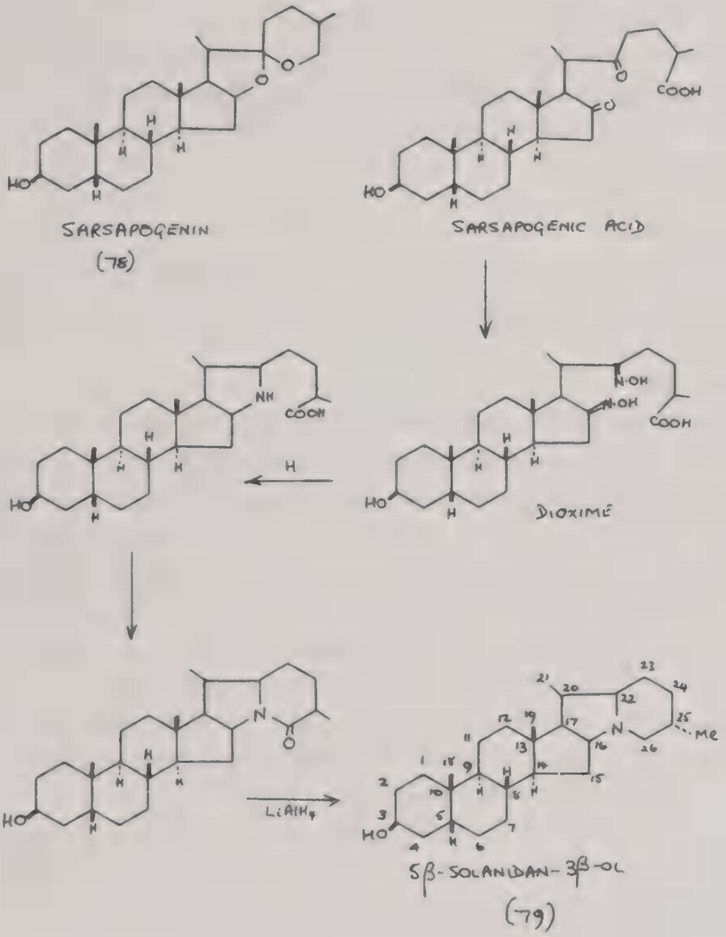
This hypothesis received strong support from the production of Diels's hydrocarbon, γ-methyl-1,2-cyclopentenophenanthrene (76) on dehydrogenation of solanidine[59] and solanidene (the product of dehydration of the alkaloid.)[75] The basic product in this reaction is 2-ethyl-5-methylpyridine (77) and the formation of these materials led to the advancement of structure (75) for solanidine,[59] the hydroxyl group being so placed by analogy with the steroid alcohols. Confirmation of this structure has been obtained by partial synthesis of 5-β-solanidan-3β-ol (79) from sarsapogenin (78) as shown,[60, 82] a sequence that also establishes the stereochemistry of (79) at carbons 3, 5, 8, 9, 10, 13 and 14 and suggests that the C-25 methyl group occupies the stable equatorial position.

Isorubijervine (80)

Isorubijervine, the product of hydrolysis of isorubijervosine from *Veratrum viride* and *V. album*, has the composition $C_{27}H_{43}O_2N$ and contains a reducible double bond, one primary and one secondary hydroxyl group and a tertiary nitrogen. Oppenauer oxidation of the base gives an α,β-unsaturated ketone reducible to a mixture of two epimeric α,β-unsaturated alcohols, neither of which is identical with isorubijervine and one of which gives a precipitate with digitonin.[31] In these respects it resembles solanidine, but whereas solanidine gives 2-ethyl-5-methylpyridine (77) and γ-methyl-1,2-cyclopentenophenanthrene (76) on selenium dehydrogenation, isorubijervine gives 2-ethyl-5-methylpyridine (77) and 1,2-cyclopentenophenanthrene (76 without the methyl group) under the same conditions[31] and this leads to



(75) (76) (77)



SARSAPOGENIN (78)

SARSAPOGENIC ACID

DIOXIME

5β-SOLANIDAN-3β-OL (79)

the formulation of isorubijervine as (80).[31, 66] This is confirmed by the oxidation of dihydroisorubijervine to an aldehyde that on Wolff–Kishner reduction gives solanidan-3β-ol (dihydrosolanidine),[83] and by the conversion of rubijervine to the quaternary salt (81, A = p-$C_6H_4SO_2$—), the iodide from which on reduction with sodium and alcohol gives solanidine (82).[55, 83] The —CH_2OH must thus be relatively close in space to the nitrogen and cannot be at C-10, and the positions C-20 and C-25 for this group can also be eliminated since (77) is formed on selenium dehydrogenation of the base. Moreover rings D and E must be *cis* fused, with C-18 and the nitrogen atom also on the same side of the molecule and the expanded stereochemistry shown in (80) and (82) can be assigned to isorubijervine and solanidine respectively.

Demissidine

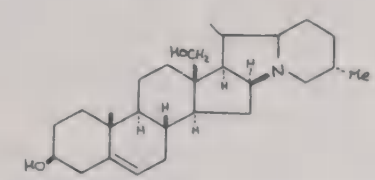
This base, the aglycone of the alkaloid demissine, is identical with dihydrosolanidine (solanidan-3β-ol) and has a *trans* A/B ring fusion.

Solasodine (85)

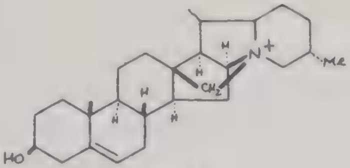
This base, which is obtained by the hydrolysis of the primary alkaloids solasonine, solasodamine and solamargine, is a secondary base containing one alcoholic hydroxyl group and has the composition $C_{27}H_{43}O_2N_7$ but has only one double bond and must thus be hexacyclic.

Like solanidine and isorubijervine it may be oxidized to an α,β-unsaturated ketone and this gives on reduction a pair of epimeric α,β-unsaturated alcohols one of which gives a precipitate with digitonin but neither of which is identical with the original base.[12, 62] These reactions suggest a similarity in structure to solanidine and this is further supported by the selenium dehydrogenation of the base to γ-methyl-1,2-cyclopentenophenanthrene (76).[61]

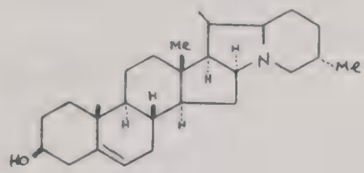
Stepwise reduction of the base catalytically affords a dihydro base, solasodan-3β-ol, analogous to dihydrosolanidine and identical with soladulcidine (from the alkaloids α-, β- and γ-soladuline), and a tetrahydro base, dihydrosolasodan-3β-ol. Lithium aluminium hydride reduction however affords a different dihydro compound, dihydrosolasodine, which may be catalytically reduced to the same tetrahydro base. Dihydrosolasodine is a stronger base than solasodine or soladulcidine and it contains two alcoholic groups forming a *O,O,N*-triacetyl



(80)



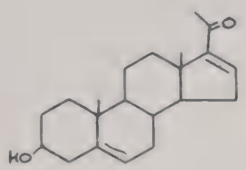
(81)



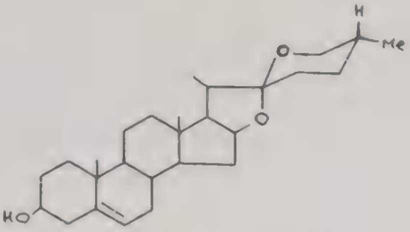
(82)

derivative.[10, 11, 12, 62] These reactions indicate that the non-alcoholic oxygen and the nitrogen are closely associated in the alkaloid and the oxygen atom must be part of a readily hydrogenolysed ring.

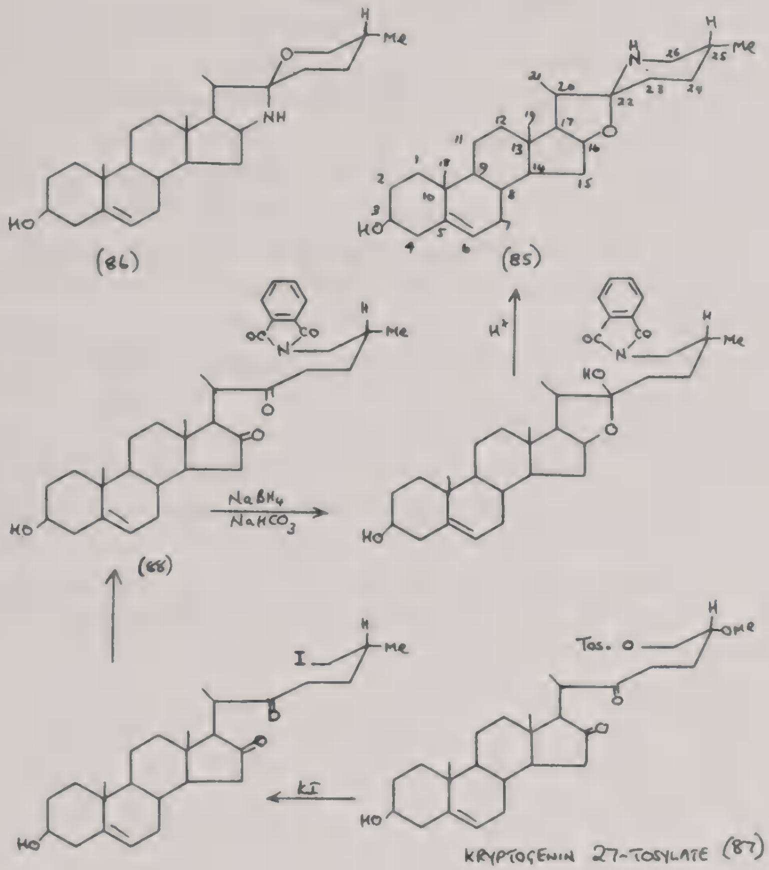
Oxidation of *O*-acetylsolasodine leads, after hydrolysis, to pregna-5,16-dien-3β-ol-20-one of certain structure (83)[66] and *N*-nitrososolasodine with acid gives a poor yield of the sapogenin diosgenin (84).[13, 65] These reactions, which define the stereochemistry of rings A, B, C, and D give no conclusive indication of the nature of the nitrogen-containing portion of the molecule, but they did lead to the proposal of the structure (85)[10] for solasodine, though clearly the alternative (86) is equally compatible with the evidence.[50] The formation of 2-ethyl-5-methylpyridine however, during the selenium dehydrogenation of solasonine, the parent of glycoside of solasodine, rules out the latter structure,[9] and the structure (85) for the base has finally been confirmed by partial synthesis from kryptogenin 27-tosylate (87) as shown opposite.[81]



(83)



DIOSGENIN (84)



(86)

(85)

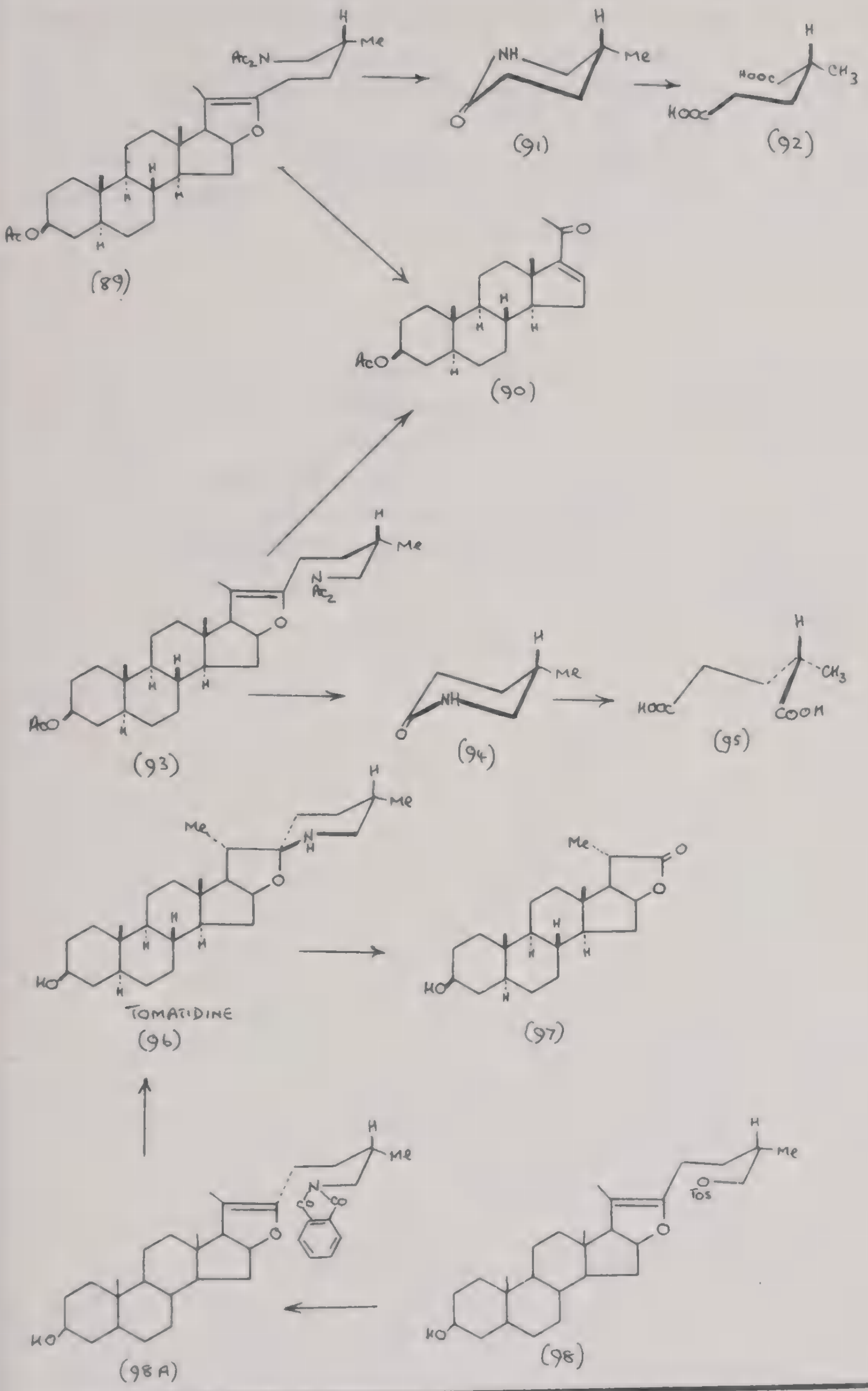
(88)

KRYPTOGENIN 27-TOSYLATE (87)

Vigorous acetylation of solasodin-3β-ol (soladulcidine) gives a triacetyl derivative (89) which on oxidation gives 3β-acetoxy-5α-pregn-16-en-20-one (90) and (*R*)-(+)-5-methylpiperidone (91), further degradable to (*R*)-(+)-α-methylglutaric acid (92).[69] Accordingly the stereochemistry of C-25 can be deduced.

Tomatidine (96)

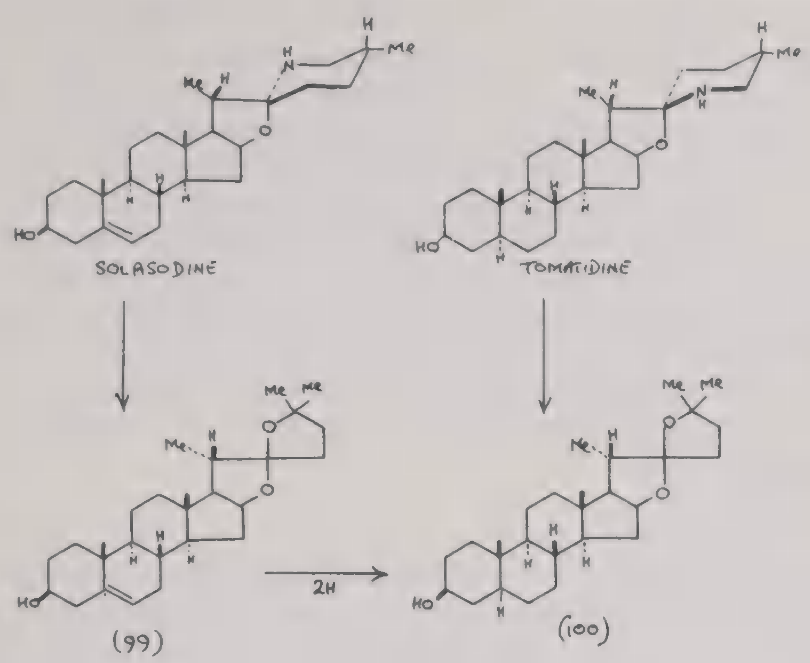
The alkaloid tomatine, $C_{27}H_{45}O_2N$, from a number of wild tomato species, on hydrolysis affords the base tomatidine, which contains one hydroxyl group and one secondary amino group and is isomeric with soladulcidine, the product of mild reduction of solasodine. Most of the reactions of tomatidine parallel those of solasodine, e.g. reduction catalytically or with lithium aluminium hydroxide gives a dihydro base analogous to dihydrosolasodine and dihydrosolasodan-3β-ol, with the second of which it is isomeric; vigorous acetylation affords a triacetyl compound isomeric with (89) which must be formulated as (103) since on oxidation it is converted into the same nitrogen-free compound (90) as is obtained from soladulcidine (89) together with (*S*)-(–)-5-methylpiperidine (94). The last of these is the enantiomorph of (91) and is degradable further to (*S*)-(–)-α-methylglutaric acid (95).[69] Tomatidine is thus seen to be (96), being a diastereoisomer of solasodan-3β-ol differing probably only in the stereochemistry of the nitrogen-containing portion of the molecule, and this is confirmed by the oxidation of diacetyltomatidine to tigogenin lactone (97) and by partial synthesis of the base itself from 27-toluenesulphonyl-ψ-neotigogenin (98) as shown opposite.[81]


(89)
(90)
(91)
(92)
(93)
(94)
(95)
TOMATIDINE
(96)
(97)
(98A)
(98)
Ac₂N
AcO
HOOC
CH₃
COOH
Me
Tos
HO

It will be seen that the triacetyl compounds (89) and (93), because of the double bond, contain two fewer asymmetric centres than do soladulcidine and tomatidine, their respective parent bases; but that these bases do differ only at C-22 and C-25 and not at C-20 is demonstrated by the conversion of *N*-nitrososolasodine into diosgenin (84) together with the spiro-epoxide (99), the dihydro derivative of which (100), having the same stereochemistry at C-20, is directly accessible from tomatidine.[65]

Solanocapsine (101)

Solanocapsine, which is structurally closely related to the other bases in this group, appears to occur uncombined in *Solanum pseudocapsicum*. It has the composition $C_{27}H_{46}O_2N_2$ and contains one primary and one secondary amino group, one hydroxyl group and a relatively unreactive second oxygen atom, and since it contains no double bonds must be hexacyclic. It clearly belongs to the steroid group, for it yields Diels's hydrocarbon (76) and 2-ethyl-5-methylpyridine (77) on dehydrogenation with selenium.[1, 67]



SOLASODINE

TOMATIDINE

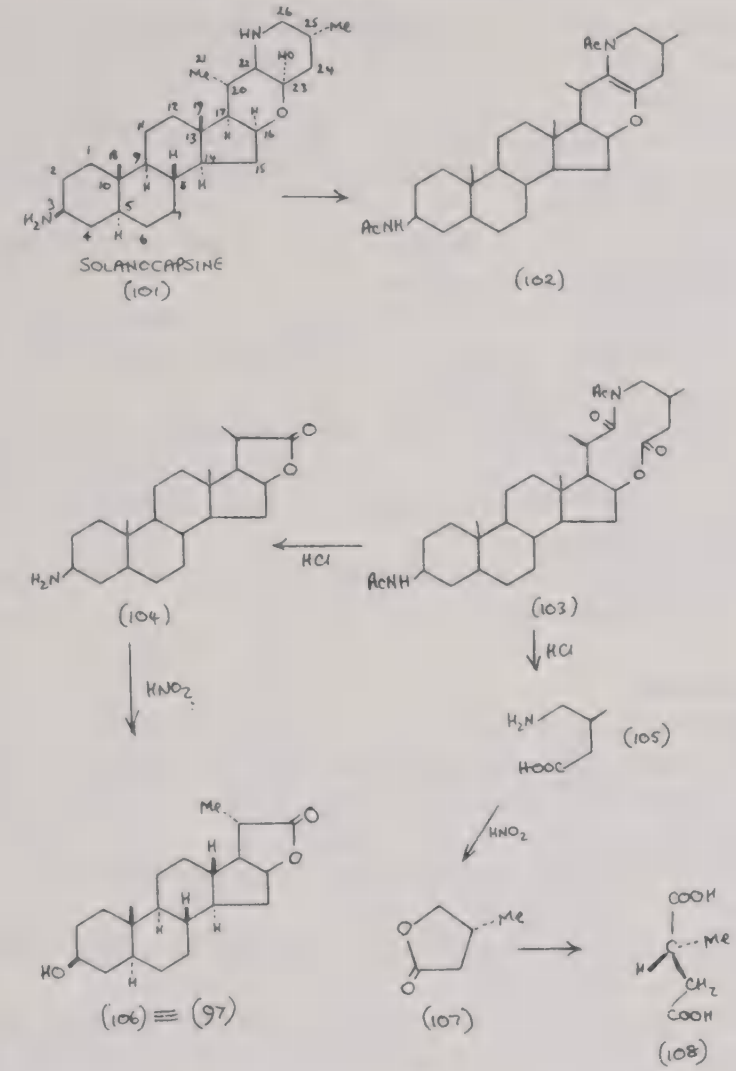
(99)

(100)

The structure of the base is revealed by the following sequence of degradations. Acetylation and dehydration of the alkaloid affords an unsaturated base which on oxidation affords a large-ring lactone-amide that on hydrolysis gives 3-deoxy-3β-aminotigogenin lactone (104) and the amino acid (105). The structure and stereochemistry of (104) are demonstrated by conversion into tigogenin lactone (106), identical with (97) obtained from tomatidine[72] and (105) on deammination gives the lactone (107) which can be oxidized to D-(+)-α-methylsuccinic acid (108).[73] Accordingly, solanocapsine can be assigned the full structure and stereochemistry (101) and the degradation products are represented by (102) and (103). It will be seen that in this base the C-16 oxygen atom is linked to C-23 instead of C-22 as in solasodine and tomatidine.

Stereochemistry of the Group

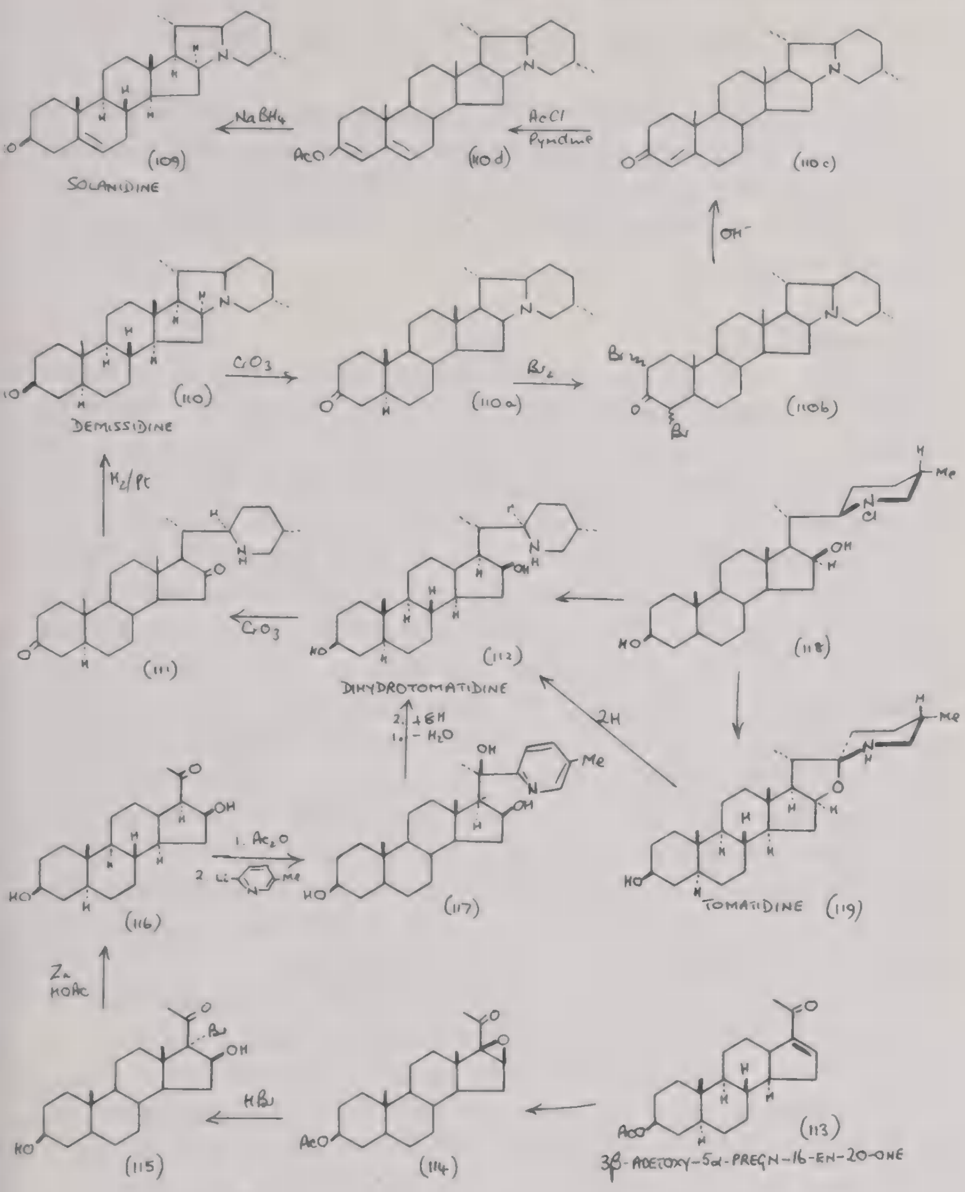
The bases of this group are all closely related stereochemically and though the stereochemistry of the individual bases is discussed above, the relationships, which have been elucidated by the degradation of bases to and synthesis from steroids of known configuration and by interconversions between the bases may be summarized here.


SOLANOCAPSINE
(101)
(102)
(103)
(104)
HCl
HCl
HNO₂
(105)
HNO₂
(106) ≡ (97)
(107)
(108)
H₂N
AcNH
AcN
HN
HO
Me
HOOC
COOH
CH₂

1. Solanidine (109) can be synthesized from sarsapogenin (77) and must thus have the stereochemistry shown at positions 3, 5, 8, 9, 10, 13 and 14.
2. Isorubijervine can be converted into solanidine and also into the quaternary salt (81), thus fixing the configurations of positions 13, 16 and 17 of (109).
3. Demissidine (110) is dihydrosolanidine and thus has the same stereochemistry as solanidine.
4. Tomatidine must have the stereochemistry shown at all points except positions 6 and 17 since the acetyl compound (93) is oxidized to (90) and (94).
5. Tomatidine can be converted into demissidine as shown in formulae (119) → (112) → (111) → (110)[47] thus fixing the configuration of demissidine at positions 4, 22, and 25 and also of tomatidine at positions 16 and 17.
6. Solanocapsine, which is degraded to (106) and (107) must have the stereochemistry shown in (101).

Total Synthesis

1. Dihydrotomatidine (112) and the diastereoisomeric dihydrosoladulcidine can be synthesized from 3β-acetoxy-5α-pregn-16-en-20-one (113), which is derivable from total steroid synthesis, as shown in (113) → (117) → (112).[70]
2. Dihydrotomatidine can be converted into demissidine by the route (112) → (111) → (110).[47]
3. Demissidine can be transformed into solanidine by the processes shown in (110) → (110a) → (110d) → (109).[74]
4. Dihydrotomatidine (112) and the diastereoisomeric dihydrosoladulcidine differing from (112) only at C-22 and C-25 can be oxidized to tomatidine (119) and soladulcidine by *N*-chlorination to (118) and treatment of this product with sodium methoxide; the reaction probably proceeds through the unstable —C=N— compound.[71]


SOLANIDINE
(109)
NaBH4
(110d)
AcCl
Pyridine
(110c)
OH⁻
DEMISSIDINE
(110)
CrO3
(110a)
Br2
(110b)
H2/Pt
(111)
CrO3
DIHYDROTOMATIDINE
(112)
(118)
2H
2. +2H
1. −H2O
(116)
1. Ac2O
2. Li–pyridyl–Me
(117)
TOMATIDINE (119)
Zn
HOAc
(115)
HBr
(114)
(113)
3β-ACETOXY-5α-PREGN-16-EN-20-ONE

VERATRAMINE, JERVINE, CEVINE GROUP

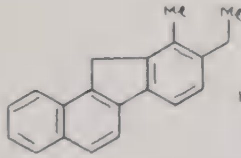
A number of bases containing 27 carbon atoms have been isolated as glycosides or esters from various *Veratrum, Sabadilla* and *Zygadenus* species. These form a closely related group of derivatives of a modified steroid skeleton. A review of the bases of this group has been given by Morgan and Barltrop.[54]

Veratramine (122)

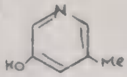
This base, the hydrolysis product of veratrosine which is its D-glucoside,[29] has the composition $C_{27}H_{39}O_2N$ and contains the following detectable groups; one secondary amino group, two secondary alcoholic hydroxyl groups, one reducible double bond, four *C*-methyl groups and an aromatic nucleus, and must therefore be pentacyclic. The C_{27} composition suggests that the base might possibly be a steroid derivative like solanidine, solasodine and solanocapsine, and this is supported by the fact that it can be shown to contain the system HO—C—C—C=C, by Oppenauer oxidation to an α, β-unsaturated ketone, O=C—C=C—C, and the reduction of this to two epimeric alcohols HO—C—C=C—C, isomeric with the starting material, which are clearly allylic alcohols.[37] Moroever the double bond must be in the system HO—C—C—C(=CH)—C since oxidation gives a vicinal glycol in which one hydroxyl group is clearly tertiary.[78] Further support for this view comes from a comparison of molecular rotation differences of veratramine and its derivatives with the corresponding differences for similar changes in the steroid group.

The presence of an aromatic nucleus in the base is demonstrated by nitration, reduction, diazotization and coupling with β-naphthol to give an azo dye,[32] and the substitution pattern of this nucleus is shown by the oxidation of veratramine to benzene-1,2,3,4-tetracarboxylic acid.[89] Triacetyldihydroveratramine may be oxidized to an aromatic ketone identical with a base obtainable from jervine and thus must contain CH_2 linked directly to the aromatic nucleus.

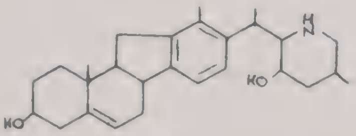
Selenium dehydrogenation of veratramine gives the 1,2-benzofluorene derivative (120) and 2-hydroxy-5-methylpyridine (121) which between them contain 26 of the 27 carbon atoms of the original base. The 27th carbon is probably an angular methyl between rings A and B of (120) extruded during aromatization and this leads to the structure



(120)



(121)



VERATRAMINE (122)

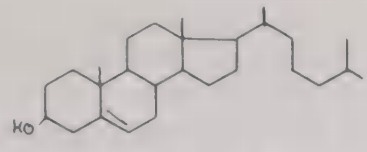
(122) for veratramine, in which the carbon atoms are numbered to correspond with those in cholesterol (123), the relationship of which to the alkaloid is thus obvious.[36, 37, 78]

The aromatic ketone obtained by the oxidation of triacetyldihydroveratramine (which is also obtainable from jervine (see next section) must thus have the structure (124);[84] the principal product of this hydrogenation, however, is the ketoepoxide (125) which is convertible by alkali into the α-naphthol derivative (126).[28]

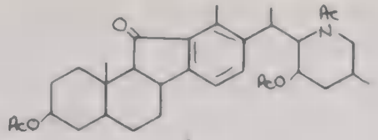
Jervine (129)

This base has been isolated directly from *Veratrum album*. It has the composition $C_{27}H_{39}O_3N$, contains one secondary amino group, one secondary hydroxyl group, two double bonds one of which is present in an α,β-unsaturated ketone system and a third, inactive ether oxygen and must thus be hexacyclic. Jervine, like veratramine, can be oxidized to a base, Δ^4-jervone, which may be reduced to Δ^4-jervine, isomeric with jervine and showing the characteristic properties of an allylic alcohol,[33, 35] and the alkaloid may thus be assumed to have a Δ^5-3-hydroxysteroid type of structure. This is supported by the oxidation of jervine to a hydroxy unsaturated 7-carbonyl compound indicating further that the isolated double bond is flanked by a methylene group.[88]

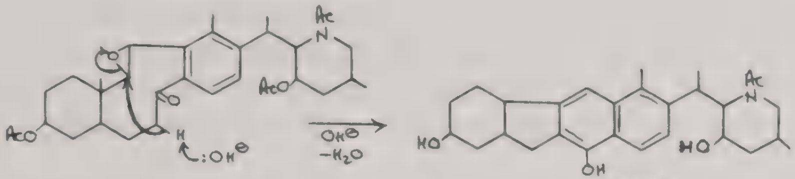
O,N-Diacetyljervine on treatment with sulphuric acid and acetic anhydride in part suffers rupture of the cyclic ether system giving a pentacyclic *O,O,N*-triacetyl compound containing an aromatic nucleus,



CHOLESTEROL (123)



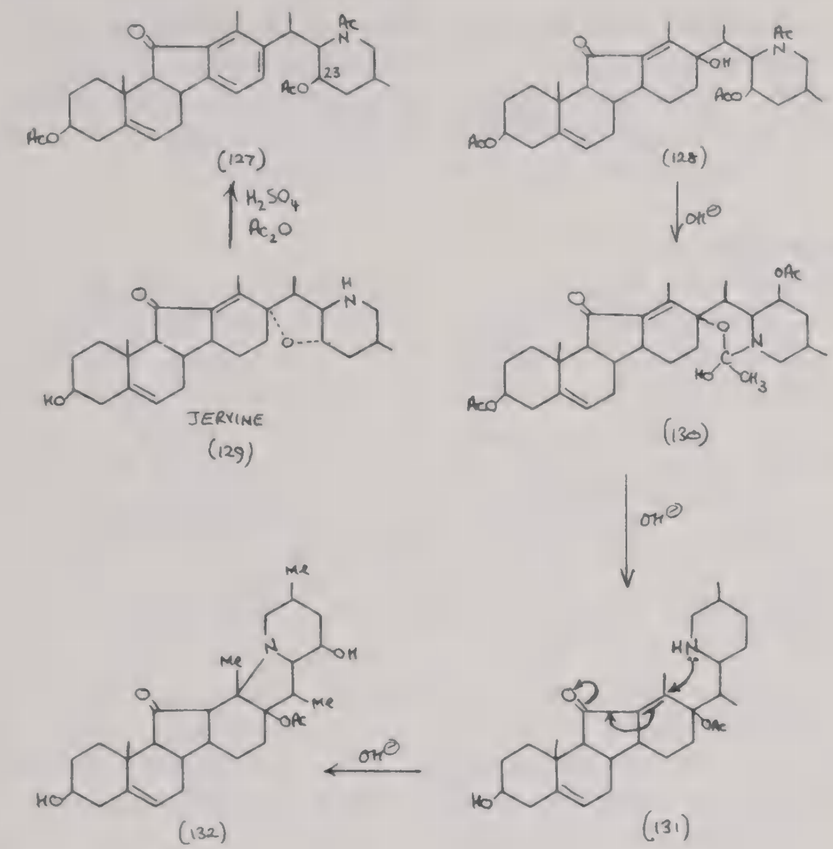
(124)



(125) (126)

and this must have the structure (127), since on reduction it is converted into the ketone (124), obtainable from dihydroveratramine. It may be deduced that C-23 is linked in jervine through oxygen to some point in ring D, and that fission of this linkage results in a hydroxyl group and a cyclohexadiene system which is then aromatized either by oxidation by the acid or by disproportionation. The principal product of acetic anhydride–sulphuric acid treatment of diacetyljervine, is, however, a non-aromatic hydroxytriacetyl compound in which the hydroxyl group resists acetylation and is thus tertiary, and which must have the hydroxyl group at C-13 or C-17; of these possibilities C-17 is preferred since then the compound, which may be assigned structure (128), is an allylic alcohol and the vinylogue of an α-hydroxyketone, and loss of water with the eventual production of (127) is readily understood.[23, 85, 86]

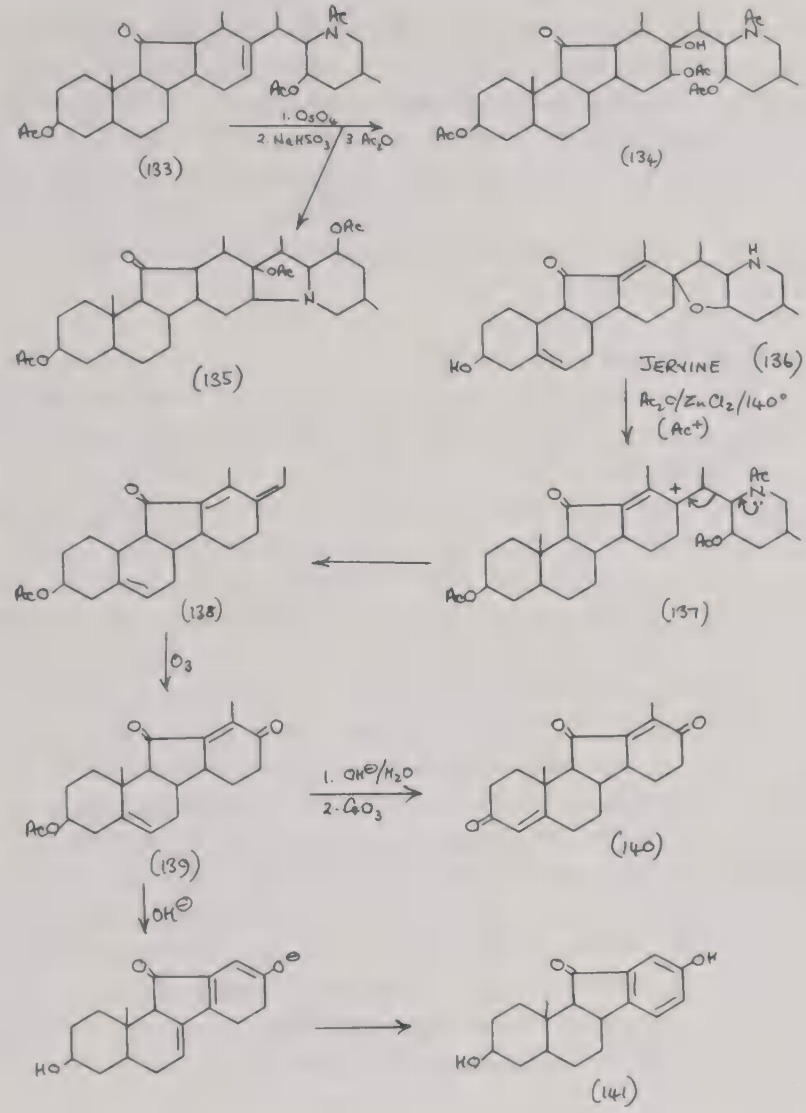
On this basis, therefore jervine must be assigned the constitution (129) and this is supported by the following evidence. The triacetyl compound (128) on treatment with alkali gives jervisine-17-acetate (132) presumably by way of the intermediates shown opposite.[68, 69]


AcO
Ac
N
23
AcO
(127)
H_2SO_4
Ac_2O
AcO
OH
Ac
N
AcO
(128)
$OH^{\ominus}$
HO
H
N
JERVINE
(129)
OAc
AcO
N
HO
CH_3
(130)
$OH^{\ominus}$
HN
OAc
HO
(131)
$OH^{\ominus}$
Me
N
OH
Me
Me
OAc
HO
(132)

Tetrahydrojervine with sulphuric acid/acetic anhydride gives (133), which with osmium tetroxide, reduction and acetylation affords (134) and (135).[90] Jervine can be split by acetic anhydride and zinc chloride at 140° as shown in (136) → (138) and the neutral product (138) can be transformed into the ketones (139), (140) and (141).[23]

Isojervine (149)

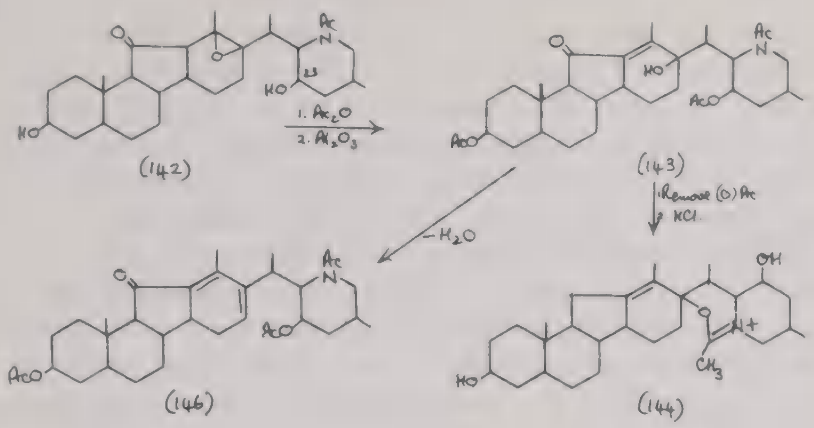
This base is the nitrogenous product of hydrolysis of the glucosidic alkaloid pseudojervine, and is also obtainable from jervine by treatment with methanolic hydrogen chloride.[30] It is isomeric with jervine, but contains a second, acetylatable, hydroxyl group and presumably is a product of ether-ring fission and may be assumed to have a hydroxyl group at C-23 and a new double bond in ring D. One double bond must be present at position 5,6 since *N*-acetylisojervine can be oxidized to *N*-acetyl Δ^4-isojervine, which is not reducible to isojervine and contains only α,β-unsaturated carbonyl groups. Isojervine itself is an α,β-unsaturated ketone but, unlike jervine, suffers reduction of the 5,6-double bond before reduction of the conjugated double bond, which must therefore occupy a different position in the two bases. Reduction of 5,6-dihydroisojervine with lithium and liquid ammonia affords the saturated ketone tetrahydroisojervine which still contains the third double bond (introduced by fission of the cyclic ether) since the *N*-acetyl compound can be epoxidized by perbenzoic acid. This epoxide


(133) (134) (135) (136) (137) (138) (139) (140) (141)

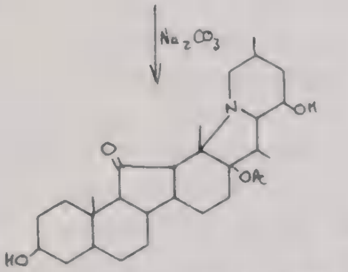
must have the structure (142), for when acetylated, adsorbed on alumina and eluted with methanol, it is converted into (143) and this may be further transformed as shown opposite into 5,6-dihydrojervisine acetate (145) available by reduction of the base (132), and the veratramine derivative (147 = 124) via (146). Tetrahydroisojervine must therefore have a double bond in the position shown in (148) and isojervine itself, which is an α,β-unsaturated ketone but not a conjugated diene, must have the structure (149).[87]

Veracevine (174) and Cevine (172)

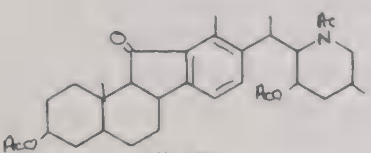
These two bases are diastereoisomers, veracevine being the alkamine that occurs naturally as the acetyl ester (cevacine), the angelyl ester (cevadine) and the veratroyl ester (veratridine). Mild hydrolysis of these bases affords veracevine, which is converted into cevagenine by more vigorous treatment with alkali, and more vigorous treatment still converts both bases into cevine. Both veracevine and cevine are hemiketals of α-hydroxy ketones and cevagenine is the free α-hydroxy ketone related to the former; the relationship is shown essentially in formulae (150) → (153). These three bases have the composition $C_{27}H_{43}O_8N$ and contain seven hydroxyl groups, a tertiary amino group not present as —NMe— and no reducible double bond; cevagenine contains a carbonyl group but veracevine and cevine do not, so cevagenine must be hexacyclic and the other two bases heptacyclic. In view of their C-27 composition and occurrence in *Veratrum* species some relationship to the steroids and the bases of the jervine–veratramine group seemed likely. This was supported by the production of 3-methylpyridine, 2-ethyl-5-methylpyridine (154), 1,2-benzohydrindane (155) and a number of hydrocarbons shown by ultraviolet studies to be derived from fluorene (156) on selenium dehydrogenation of cevine.[78, 16, 18]



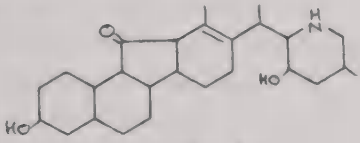
(142) (143) (146) (144)



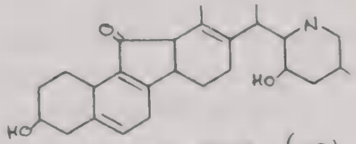
5,6-DIHYDROJERVISINE 17-ACETATE (145)



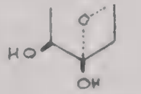
11-KETO-TRIACETYL-5,6-DIHYDROVERATRAMINE (147)



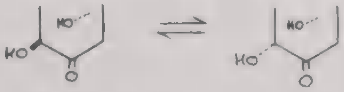
(148)



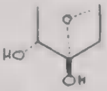
ISOJERVINE (149)



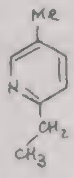
VERACEVINE (150)



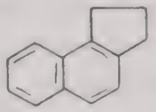
CEVAGENINE (151) (152)



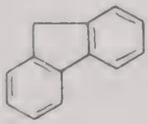
CEVINE (153)



(154)



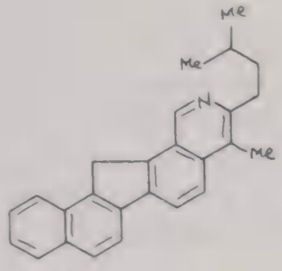
(155)



(156)

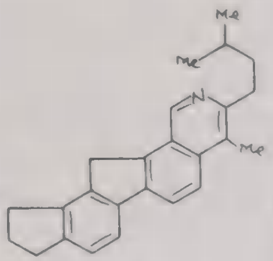
The most important products of selenium dehydrogenation, however, are the tertiary bases cevanthridine $C_{25}H_{27}N$ and veranthridine $C_{26}H_{25}N$ and of these the latter, which contains all but one of the 27 carbons of cevine, is obviously in the higher oxidation state. Both bases are clearly derivatives of fluorene and both on oxidation give fluorenones, which may be reduced to the original bases by the Huang-Minlon process. The ultraviolet spectrum shows that cevanthridine is the less conjugated of the two bases but that it is still more conjugated than fluorene; it can be reduced catalytically to a tetrahydro secondary base showing typical fluorene ultraviolet absorption. These facts can be explained by assuming that cevanthridine contains a pyridine ring fused to a fluorene system, and the ultraviolet absorption most closely accords with fusion in such a way as to give an isoquinoline rather than a quinoline system. On this basis, and the need to maintain a steroid or jervine-like fundamental skeleton, cevanthridine has been assigned the structure (157) and veranthridine the structure (158). As cevine is a hexacyclic tertiary base the skeleton (159) may logically be proposed for the hypothetical cevane, the 27th carbon being placed as an angular substituent between rings A and B.[34, 56]

The placing of the cevine oxygen atoms on the cevane skeleton has been deduced by a complex chain of reasoning in the following way. Oxidation of cevine with chromic acid gives the acids (160), (161) and (162). Of these (160) can be converted into the dianhydride which on pyrolysis gives the ketone anhydride identified by synthesis. On pyrolysis (162) loses two moles of water yielding decevinic acid (163), the structure of which is clearly demonstrated by the degradation shown opposite to (+)-9-methyl-*cis*-decalin-1-carboxylic acid (168), prepared by synthesis and related to the A/B system of the steroids and triterpenes.[4, 20, 24, 39, 54] From the production of the acid (162) it may be concluded that cevine contains oxygen substituents at positions 3, 4, and 9 but not at positions 1, 2, 5, 6, 7, 8 or 11. No oxygen substituents are present at positions 23 or 27, since (*R*)-(+)-5-methylpiperidin-2-one can be obtained by oxidation of cevine,[17, 41] nor at C-18 or 22, as cevine is not a carbinolamine; this leaves positions 12, 13, 14, 15, 16, 17 and 20 for five remaining hydroxyls.



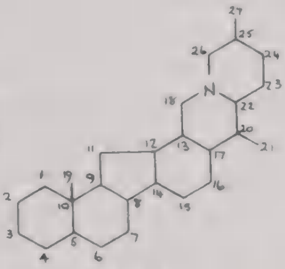
VERANTHRIDINE

(158)



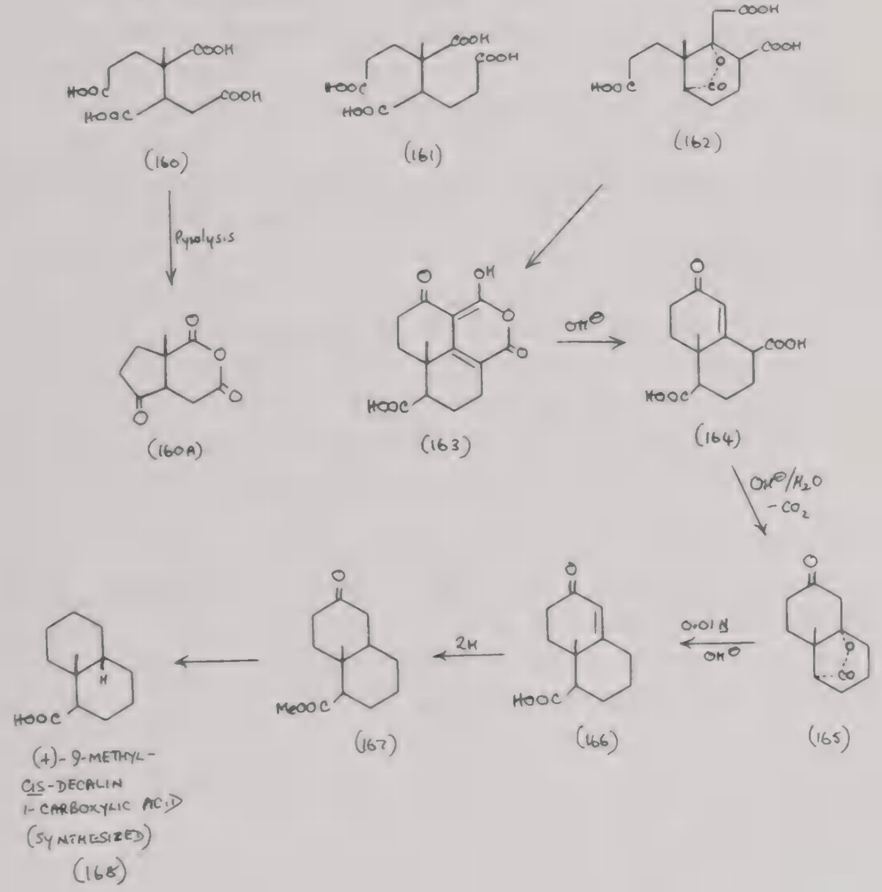
CEVANTHRIDINE

(157)



CEVANE

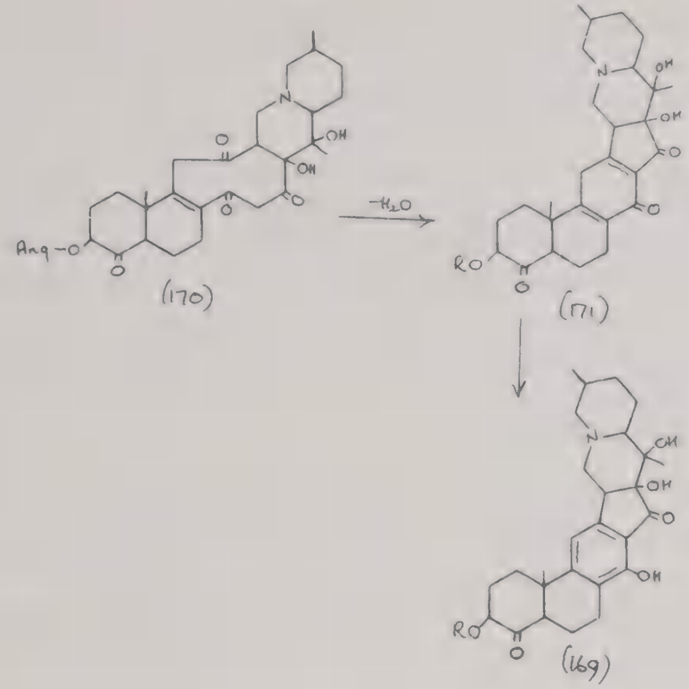
(159)



Cevine contains a ditertiary-α-glycol system that is oxidized by periodic acid with consumption of only one mole of oxidant, indicating that this system cannot be flanked by —C(OH)—. This system can also be incorporated into two different orthoacetate esters, in one of which the third oxygen atom is at position 9, and this glycol system is accordingly located at positions 12 and 14. This implies that positions 13 and 15 must be hydroxyl free and accordingly, the three remaining hydroxyl groups must be at positions 16, 17, and 20, and the resistance of this α,β,γ-triol system to periodic acid oxidation must be due to steric hindrance.

Support for this assignment is forthcoming from the following facts. When the C-9 hydroxyl is otherwise bound up an orthoacetate system involving the 12, 14, and 17 hydroxyls can be formed and the resulting ester can be oxidized to a C-16 ketone with a normal six-ring carbonyl IR absorption (1730 cm^{-1}), whereas the hydrolysis product, with a C-17 hydroxyl, has IR absorption at 1702 cm^{-1} as a result of hydrogen bonding. Also the chromic acid oxidation of cevadine (3-angelylveracevine) gives the compound (169) presumably by way of the intermediates (170) and (171); in (169) the 7-hydroxyindan-1-one unit can be clearly identified and since enolization cannot occur there can be no hydrogen at C-17.[53] Finally selenium dehydrogenation of cevine affords, in addition to the compounds previously described, a base $C_8H_{11}ON$ which must be 2-(α-hydroxyethyl)-5-methylpyridine since it gives pyridine-2,5-dicarboxylic acid on oxidation and since cevine contains no primary hydroxyl group; this establishes the presence of hydroxyl at position 20.[4]

Cevine thus contains oxygen substituents at positions 3, 4, 9, 12, 14, 16, 17, and 20. Positions 9 and 4 are involved in a hemiketal system which constitute the required seventh ring in cevine and veracevine; this has been confirmed by periodate fission of cevine 12,14,17-orthoacetate to an aldehydro-γ-lactone (171).[2, 3] Thus cevine may be


Ang–O
(170)
$-H_2O$
RO
(171)
RO
(169)
OH
O

represented by the structure (172) and cevagenine by (173); veracevine is epimeric with cevine at C-3 (174). The stereochemistry shown in these structures is supported as follows:

Rings A/B The A/B system must be a *cis* decalin in order that the 4,9-ether bridge can exist in cevine and veracevine, and for the same reason the ether bridge itself must be *cis* and on the opposite side of the molecule to the 10-methyl group. The 3-hydroxyl group must be axial in veracevine and equatorial in the more stable cevine. In cevagenine the A/B junction has the more stable *trans* arrangement, in which case the 3-hydroxyl group can remain *cis* to the 10-methyl and yet have the stable equatorial configuration.

Rings B/C/D The oxygen substituents at positions 9, 12, 14 and 17 must all be *cis* since only then can both 9,12,14- and 12,14,17-orthoacetates be formed. The 16-hydroxyl is *trans* to that at C-17 since the C-16-epimer (obtained with the normal compound by reduction of the corresponding ketone) is oxidized by periodic acid more rapidly than the normal compound.[45]

Rings E/F All derivatives of cevine having free hydroxyl groups only at C-17 and C-20 are stable to glycol-splitting agents, and this is explained by assuming that these two groups are axial and *trans*. Triacetylveracevine-D-orthoacetate can be oxidized to a carbinolamine ether involving a C-20, C-26 bridge which is only possible with an E/F junction as shown in (174).[46] The stereochemistry at C-25 is determined by the identification of (*R*)-(+)-5-methylpiperidin-2-one as one of the products of oxidation of cevine.

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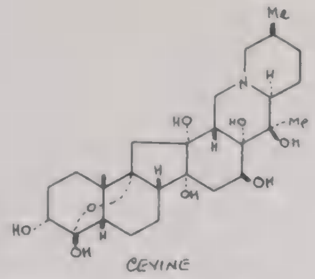
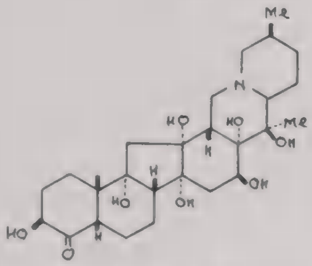


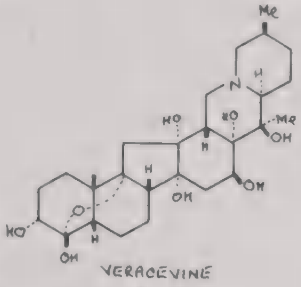
CEVINE

(172)



CEVAGENINE

(173)



VERACEVINE

(174)

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CHAPTER 6

ALKALOIDS OF THE INDOLE GROUP

Material in this chapter is supplementary to that in chapters 7 and 8 of Volume I of this series[21] and covers alkaloids of structural types not fully understood at the time of writing of that volume. A considerable amount of work has been done on alkaloids of this group, which is now seen to consist of a greater variety of structural types than any other. In recent years the classical methods of elucidation of structure have often been bypassed by the application of modern techniques such as mass spectrography, nuclear magnetic resonance studies and x-ray crystallography, especially in the indole alkaloid field, and this account includes examples of the use of these methods.

Representative bases of all the structural types will be discussed and the structural variations within the groups indicated, in the following order.

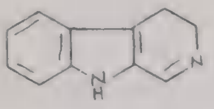
1. Evodiamine and related bases.
2. Tuberostemmonine.
3. Uleine and ellipticine.
4. Flavopereirine.
5. Ajmalicine and mitraphylline.
6. Akuammicine and related bimolecular bases.
7. Aspidospermatine and condylocarpine.
8. Ajmaline and related alkaloids, including the bimolecular base geissolosimine.
9. Aspidospermine and its analogues.

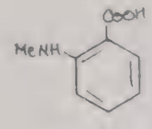
10. The iboga alkaloids.
11. Bimolecular alkaloids consisting of aspidosperma and iboga units.
12. Alkaloids of *Hunteria eburnea.*
13. Calycanthine and chimonanthine.
14. Echitamine.
15. The calabash curare alkaloids.

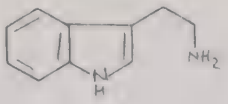
Evodiamine (4), Rutaecarpine (5) and Hortiamine (17)

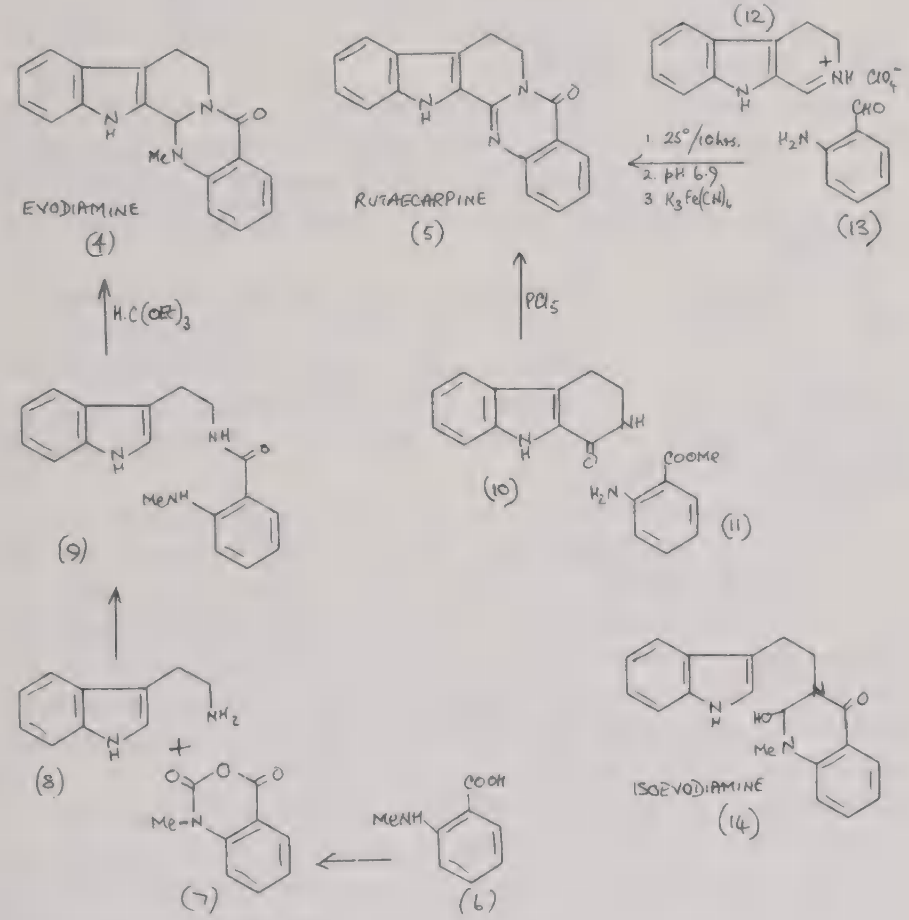
The first two of these bases, from *Evodia rutaecarpa*, the dried fruits of which comprise the chinese drug WüChü Yü, are closely related, evodiamine has the composition $C_{19}H_{17}ON_3$ and rutaecarpine is $C_{18}H_{13}ON_3$. Evodiamine is converted by ethanolic hydrochloric acid into evodiamine hydrate, also called isoevodiamine, which is transformed into racemic evodiamine by acetic anhydride at 150°. Boiling alcoholic potassium hydroxide decomposes evodiamine to dihydronorharman (1)[7] and *N*-methylanthranilic acid (2), whereas evodiamine hydrate under the same conditions furnishes *N*-methylanthranilic acid (2), carbon dioxide and 3-β-aminoethylindole (3).[5, 57] When evodiamine hydrate is heated dry it gives water, methyl chloride and rutaecarpine, which on heating with amyl alcoholic potash gives anthranilic acid and a base $C_{11}H_{12}O_2N_2$ that can be decarboxylated to the amine (3). On this evidence evodiamine was formulated as (4) and rutaecarpine as (5), and these structures have been confirmed by the synthesis of evodiamine (6) → (9) → (4)[8] and rutaecarpine (10)+(11) → (5)[6, 65] and (12)+(13) → (5).

As the transformation of evodiamine to evodiamine hydrate and back to evodiamine proceeds with racemization, the link between the asymmetric carbon and the α-position of the indole must be broken by the hydration, and isoevodiamine must have the structure (14).


(1)


(2)


(3)


(12)
NH ClO_4^-
CHO
H_2N
(13)
1. 25°/10 hrs.
2. pH 6·9
3 $K_3Fe(CN)_6$
MeN
EVODIAMINE
(4)
RUTAECARPINE
(5)
$H.C(OEt)_3$
PCl_5
NH
MeNH
(9)
NH
(10)
COOMe
H_2N
(11)
NH_2
(8)
Me-N
(7)
MeNH
COOH
(6)
HO
Me N
ISOEVODIAMINE
(14)

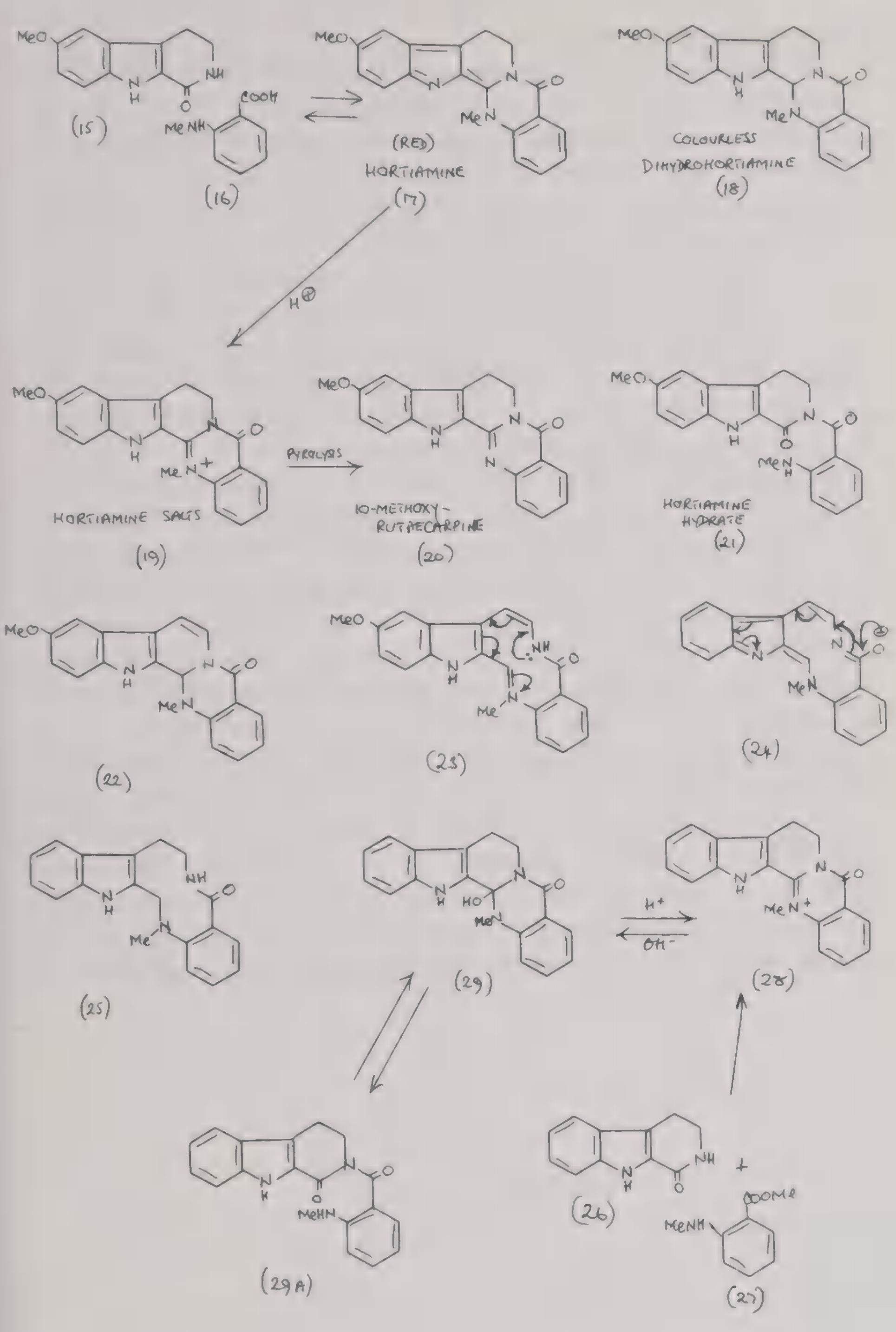
Hortiamine is a red alkaloid of composition $C_{20}H_{17}O_2N_3$ from *Hortia arborea* Engl. It is rapidly degraded in ethanolic potash to a base $C_{12}H_{12}O_2N_2$, identified by spectral studies and finally by synthesis as the methoxyketotetrahydronorharman (15), together with *N*-methylanthranilic acid (16). It is thus structurally related to the colourless evodiamine, and to account for its red colour it may be assigned the structure (17); it is obtainable from the base (15), the methyl ester of the acid (16) and phosphorus oxychloride in a manner analogous to the synthesis of rutaecarpine given above.[72]

Catalytic hydrogenation of hortiamine gives a dihydro base (18) which is colourless and which closely resembles evodiamine, of which it is the 10-methoxy derivative. The salts of hortiamine are quaternary salts (19) and on pyrolysis these are converted into 10-methoxyrutaecarpine (20).

The red hortiamine solutions fade to pale orange when allowed to stand in the presence of water, and deposit the yellow hortiamine hydrate (21), the UV spectrum of which closely resembles that of the *N*-benzoyl derivative of the base (15). This hydrate, which is the 6-methoxyderivative of the alkaloid rhetsinine (see below), can be dehydrated to hortiamine.

Acetylation of the hydrate yields a monoacetyl and a diacetyl derivative, and also a pale yellow base, isohortiamine, formulated as the amide (22); with acids this gives deep yellow salts having the resonating cation (23) and in alkalis also gives a deep yellow solution containing the resonating anion (24). Catalytic reduction of the base yields the colourless tetrahydro compound (25). A base closely resembling desmethoxyisohortiamine (from rhetsinine and acetic anhydride) has been isolated from *H. braziliana* Vel.[71]

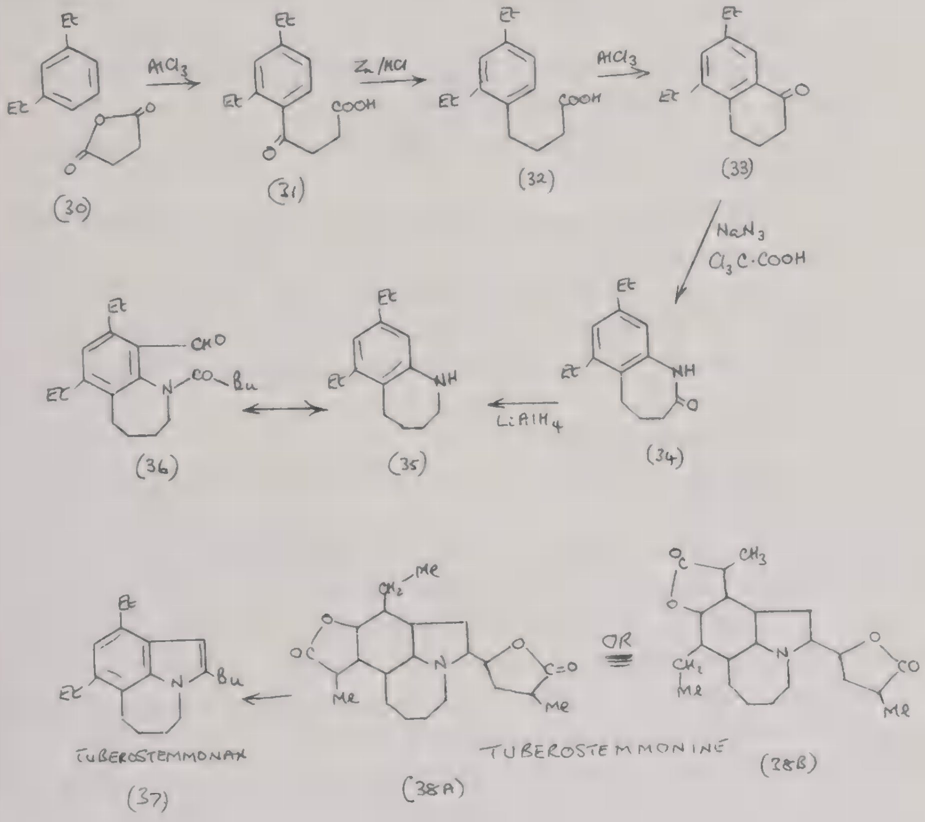
Rhetsinine is an alkaloid from *Xanthoxylum rhetsa* D.C. and is identical with material obtained by the oxidation of evodiamine, for which the carbinolamine structure (29) was first suggested, but the spectral properties of the base are more in accord with the tautomeric structure (29A). It has been synthesized as shown in formulae (26) → (29A).[73]


MeO
NH
N H
O
(15)
COOH
MeNH
(16)
MeO
N
N
O
MeN
(RED)
HORTIAMINE
(17)
MeO
N H
N
O
MeN
COLOURLESS
DIHYDROHORTIAMINE
(18)
H⊕
MeO
N H
N
O
MeN+
HORTIAMINE SALTS
(19)
PYROLYSIS
MeO
N H
N
O
N
10-METHOXY-RUTAECARPINE
(20)
MeO
N H
O
N
O
MeNH
HORTIAMINE HYDRATE
(21)
MeO
N H
N
O
MeN
(22)
MeO
N H
NH
O
Me N
(23)
N
N
O
⊖
MeN
(24)
N H
NH
O
Me N
(25)
N H
HO
N
O
MeN
(29)
H+
OH−
N H
N
O
MeN+
(28)
N H
O
N
O
MeHN
(29A)
N H
NH
O
+
(26)
COOMe
MeNH
(27)

Tuberostemmonine (38 B)

This alkaloid is found in *Stemmona tuberosa*[61, 82, 90] and has the composition $C_{22}H_{33}O_4N$. It contains two lactone rings which, from the infrared spectrum, must be five-membered. Studies of the nuclear magnetic resonance spectra of the alkaloid and its derivatives have led to an almost complete elucidation of its structure. The NMR spectrum of tuberostemmonine shows two deshielded C—CH_3 group absorptions at 8·63 and 8·77 ppm, indicating that both these groups are *alpha* to carbonyl, and a third C—CH_3 triplet at 9·02 ppm. Permanganate oxidation of the alkaloid gives 1-methylsuccinic acid and a neutral compound (NMR C—CH_3 at 8·70 (deshielded) and 9·02 ppm) indicating that the two α-CH_3 groups are on different carbon atoms and must therefore be associated with the two lactone rings.[56, 41]

The fundamental substitution pattern of the base is revealed by oxidation under mild conditions to a pyrrole $C_{22}H_{29}O_4N$[60] which has the NMR spectrum of a 2,3,5-substituted pyrrole.[41] Dehydrogenation of the alkaloid over 20% palladium/charcoal gives tuberostemmonan, $C_{20}H_{29}N$,[60] which may be oxidized to an isatin-like compound ($C_{16}H_{19}O_2N$) by chromic acid, and on ozonolysis is converted into an *N*-acylaromatic aminoaldehyde (36), the structure of which is demonstrated by conversion into butyric acid and the base (35) and by the synthesis of the last of these by the route (30) → (35).[88] This implies that tuberostemmonan must be the indole (37). On the basis of this and the requirements that both lactone carbonyls of tuberostemmonine must be α to C—CH_3 the structures (38A) and (38B) may be deduced for the parent alkaloid. Since the preparation of the manuscript of this book further NMR studies have shown that the alkaloid has the structure (38B). These alternative structures were suggested before the


Et
AlCl3
Zn/HCl
COOH
AlCl3
(30)
(31)
(32)
(33)
NaN3
Cl3C·COOH
CHO
N–CO–Bu
NH
LiAlH4
(36)
(35)
(34)
CH2–Me
OR
CH3
C=O
Me
N
Bu
TUBEROSTEMMONAX
(37)
TUBEROSTEMMONINE
(38A)
(38B)

synthesis of the base (35) on the basis of the degradations (38) → (44), each of the products of which were submitted to NMR study,[41] from which it was deduced that:

(a) (40) contains the system C=C—CH_3 (8·1 ppm) and two other C—CH_3 groups (8·81, 9·13 ppm) and a secondary —OAc group (αH, 4·81 ppm).

(b) (41) contains CH_3—CO and a secondary PhCO.O— group (αH, 2·08 ppm).

(c) (42) contains CH_3—CO—C=CH—(methyl 7·69 ppm, βH, 3·37 ppm) and two other C—CH_3 groups.

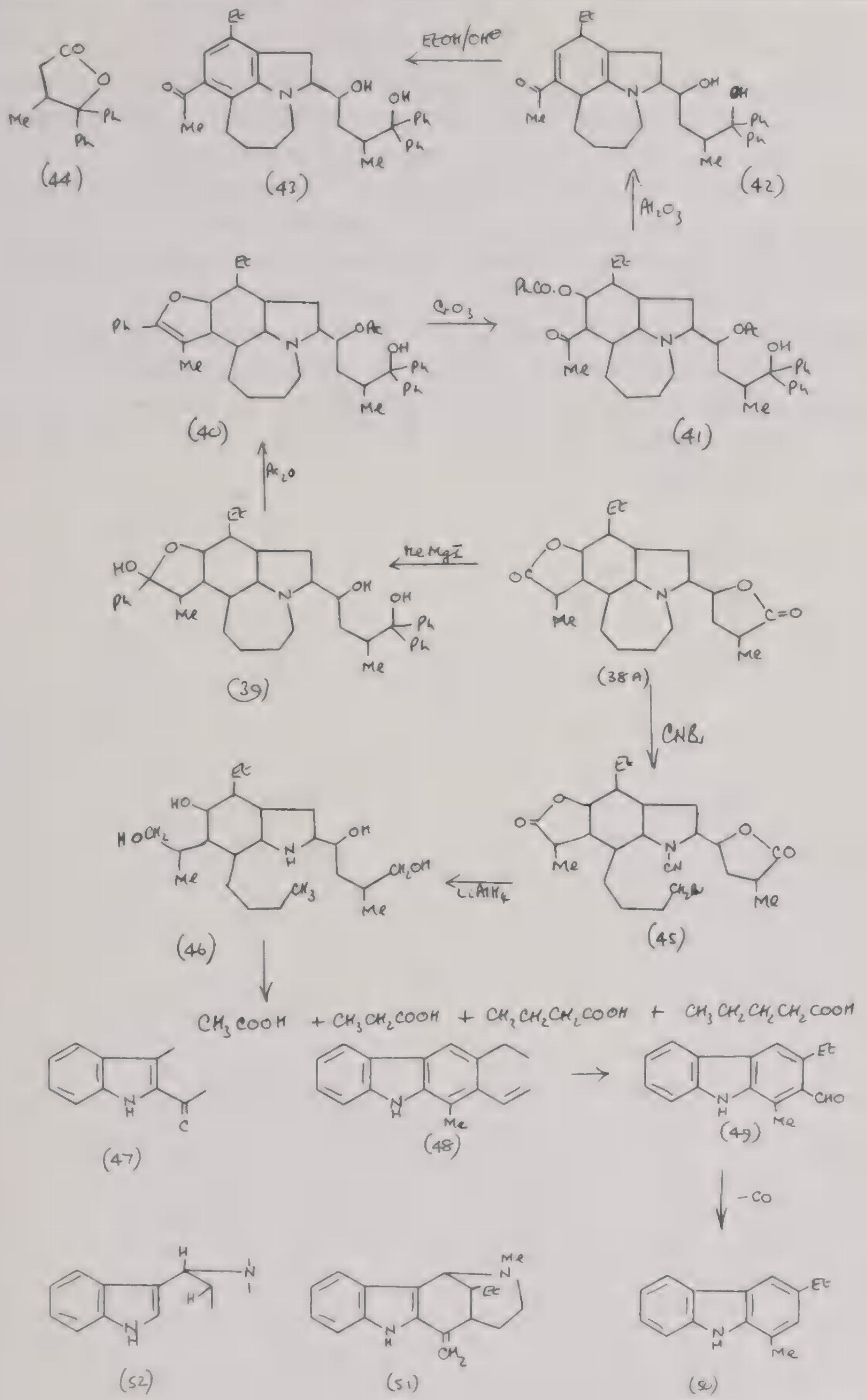
(d) (43) contains CH_3CO—Ar (7·47 ppm) and 11 aromatic hydrogens (2·49–2·77 ppm).

Reaction with cyanogen bromide transforms tuberostemmonine into the *N*-cyanobromo compound (45) and lithium aluminium hydride reduction of this (to 46) followed by oxidation gives n-valeric acid and n-butyric acid, in addition to propionic and acetic acids which are obtained by Kuhn–Roth oxidation of tuberostemmonine itself.[41]

Uleine (51) and Ellipticine (57)

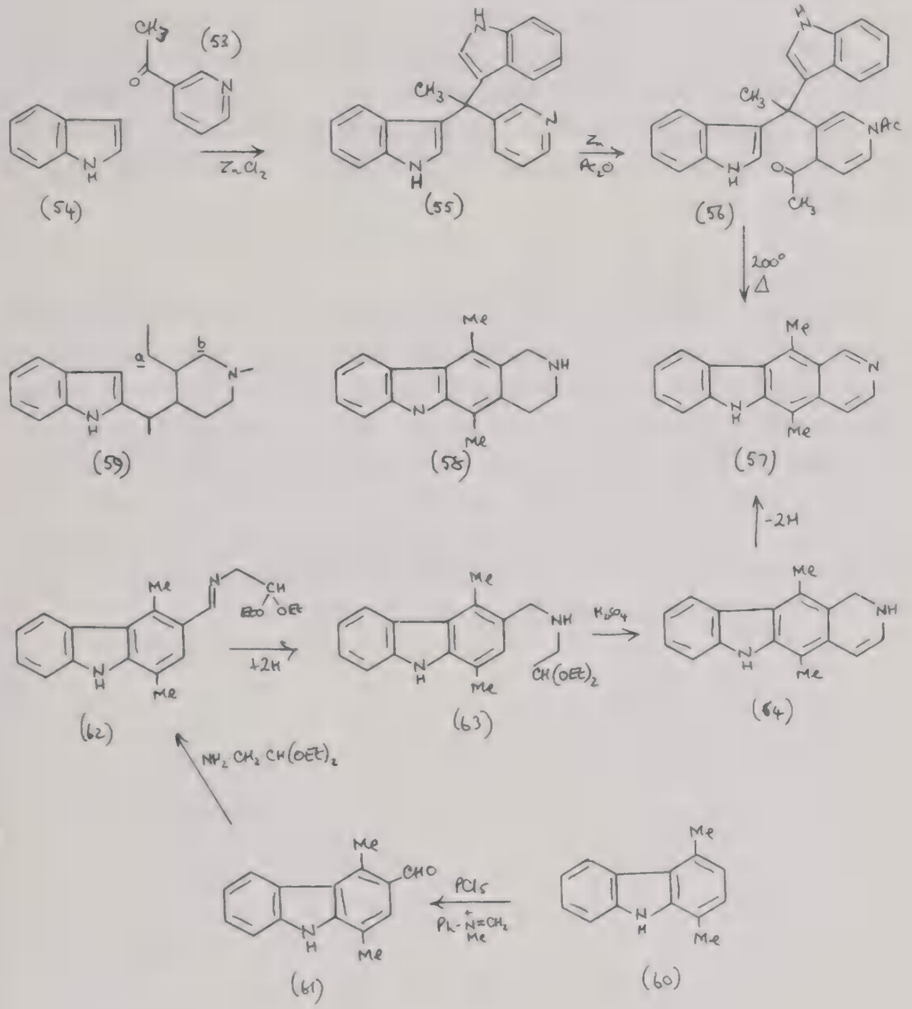
Uleine is one of the alkaloids of *Aspidosperma ulei* Mgt. and is unusual in that it has a carbon skeleton of seventeen atoms, two less than most other indole alkaloids. It has the composition $C_{18}H_{22}N_2$, and nuclear magnetic resonance studies show the presence of the following systems: —CH_2CH_3, —NMe—, —NH(indole)—, C=CH_2 and four aromatic hydrogen atoms. The ultraviolet evidence indicates that the double bond is conjugated with the indole nucleus and is linked to the α-position, leading to the part structure (47) for uleine. Exhaustive methylation proceeds through two stages, the first of which is accomplished with great ease, to give a vinylcarbazole (48), which may be converted by osmium tetroxide followed by periodic acid oxidation into an aldehyde (49), having ultraviolet absorption very similar to that of 2-formylcarbazole but different from those of 1-, 3- or 4-formylcarbazole. Decarbonylation of this aldehyde affords 1-methyl-3-ethylcarbazole (50), identical with material prepared by synthesis. As the NMR spectrum of uleine indicates the presence of the system (52) in the alkaloid, uleine is assigned the structure (51).[32] this may be compared with that of condylocarpine (142).

Ellipticine, $C_{17}H_{14}N_2$, an alkaloid from *Aspidosperma subincanum*


(44)
(43)
EtOH/OH⁻
(42)
Al₂O₃
(40)
CrO₃
PhCO.O
(41)
Ac₂O
(39)
MeMgI
(38A)
CNBr
(46)
LiAlH₄
(45)
CH₃COOH + CH₃CH₂COOH + CH₃CH₂CH₂COOH + CH₃CH₂CH₂CH₂COOH
(47)
(48)
(49)
–CO
(52)
(51)
ULEINE
(50)

(quillo-bordon), contains an indole —NH— and two —CH_3 groups according to the NMR spectrum, but as Kuhn–Roth oxidation gives no acetic acid these methyl groups are presumably attached to aromatic nuclei. The alkaloid is a tertiary base and can be reduced to tetrahydroellipticine, which is a secondary base having the ultraviolet absorption of a carbazole. On the basis of a probable skeletal relationship with uleine, the structure (57) was proposed for the base and confirmed by synthesis (53) → (57).[103] Tetrahydroellipticine is thus (58) and the relationship to uleine (51) may be seen in the skeleton of a hypothetical intermediate (59) in which linkage of the indole β-position to *a* would give (eventually) ellipticine, whereas linkage to *b* would give uleine.

A second synthesis of ellipticine (60) → (64) → (57) has recently been accomplished.[33]

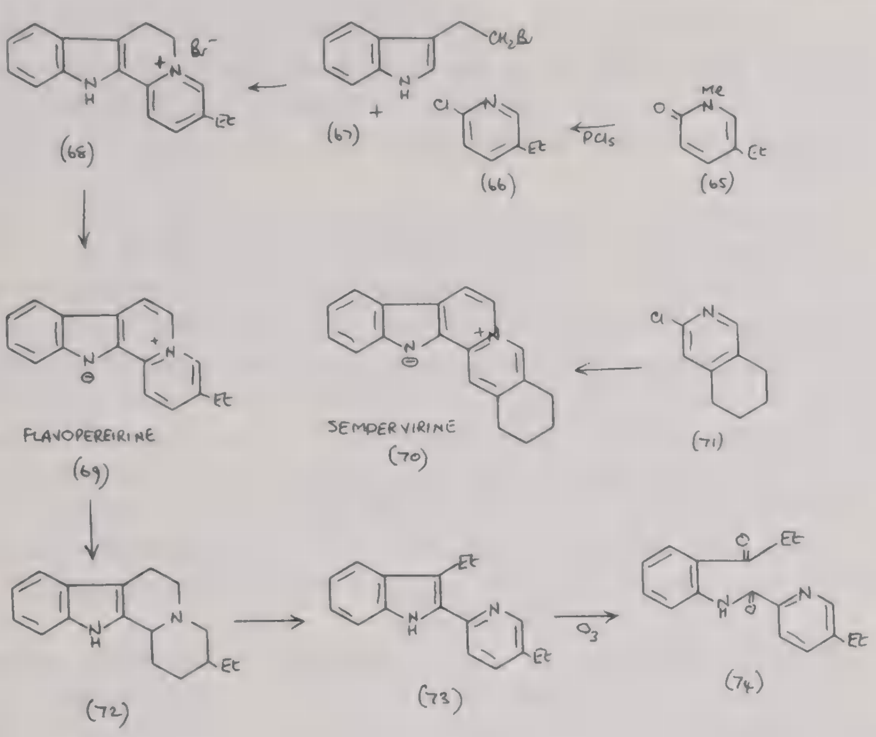

(53)
CH3
N
(54)
ZnCl2
(55)
CH3
Zn
Ac2O
(56)
NAc
CH3
200°
Δ
(59)
a
b
(58)
Me
NH
(57)
Me
-2H
(62)
Me
N
CH
EtO OEt
+2H
(63)
NH
CH(OEt)2
H2SO4
(64)
NH
NH2 CH2 CH(OEt)2
(61)
CHO
PCl5
Ph-N+=CH2 Me
(60)
Me

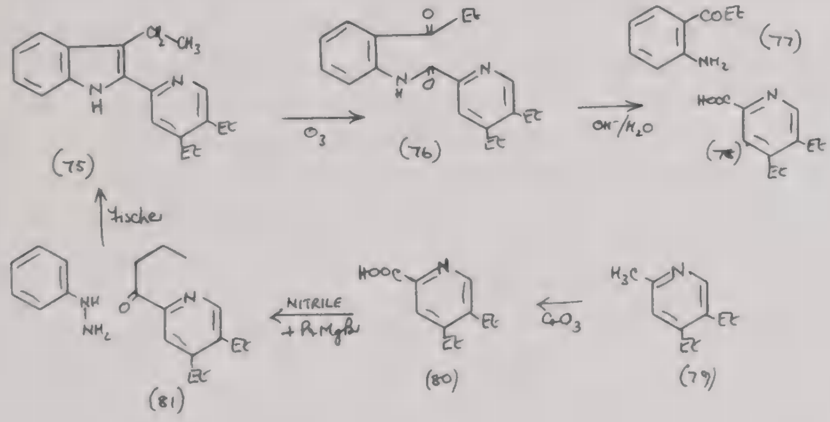
Flavopereirine (69)

Flavopereirine is an anhydronium base isolated from the bark of *Geissospermum laeve* Baillon; it has the composition $C_{17}H_{14}N_2$, being isomeric with ellipticine. Its ultraviolet spectra in acids and bases are identical with those of sempervirine (70) (see ref. 21, p. 156). It can be hydrogenated to octahydroflavopereirine (72), which on selenium dehydrogenation gives desethylalstyrine (73), a product of degradation of corynantheine, the structure of which is known from ozonolysis to (74) and hydrolysis of this to *o*-aminopropiophenone and 5-ethylpyridine-2-carboxylic acid. Flavopereirine must thus be (69),[20] and this has been confirmed by synthesis as shown in (65) → (69);[10] use of the base (71) instead of (65) in this process results in the production of sempervirine (70).[10]

Ajmalicine (82) and Mitraphylline (102)

Ajmalicine, originally named δ-yohimbine, occurs in *Rauwolfia serpentina* and other *Rauwolfia* species. Its composition is $C_{21}H_{24}O_3N_2$ and it contains one COOMe, one C—CH_3, one NH and one tertiary amino group and has the ultraviolet spectrum of an indole containing an isolated MeOOC—C=CH—O—C— system. Selenium dehydrogenation of the alkaloid affords alstyrine (75),[43] the structure of which is obvious from the results of ozonolysis to (76) and hydrolysis of this to *o*-aminopropiopheneone (77) and 4,5-diethylpyridine-2-carboxylic acid (78) and by synthesis from (79) as shown opposite.[62]


Br⁻
CH₂Br
(68)
(67)
(66)
(65)
PCl₅
Me
Et
FLAVOPEREIRINE
(69)
SEMPERVIRINE
(70)
(71)
(72)
(73)
O₃
(74)


CH₂CH₃
(75)
O₃
(76)
COEt
NH₂
(77)
OH⁻/H₂O
HOOC
(78)
Et
Fischer
NITRILE
+ PrMgBr
(81)
(80)
CrO₃
H₃C
(79)

Assuming that ajmalicine has the yohimbine carbon skeleton (supported by dehydogenation of the base to a tetradehydro base) the structure (82) may thus be assigned to it,[43] and this has been confirmed by the total synthesis of the alkaloid as shown in formulae (85) → (90) → (82).[92]

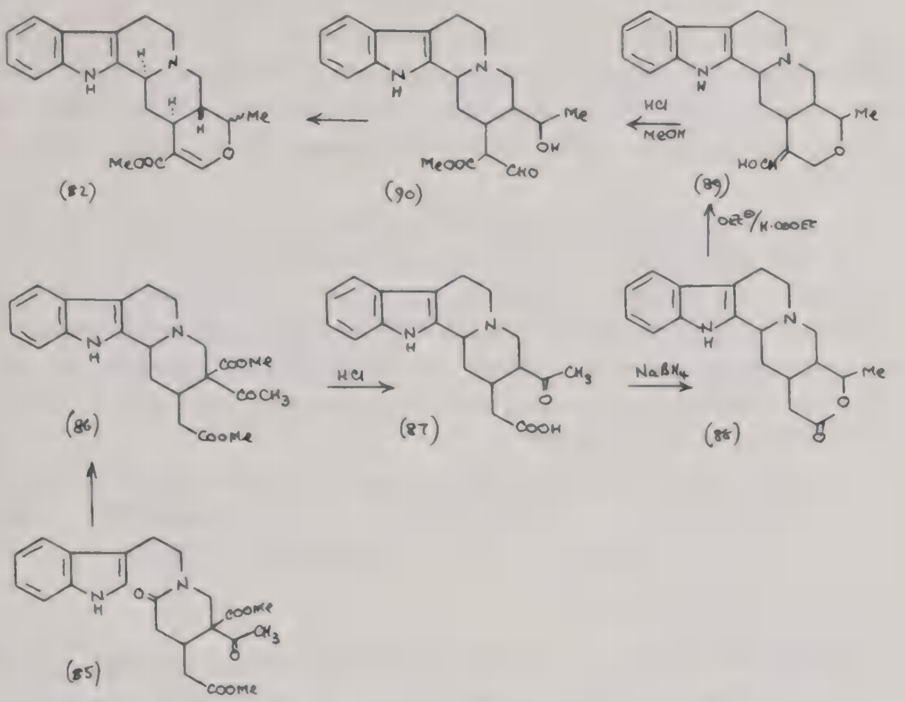
The stereochemistry assigned in structure (82) follows from a study of the oxidation of the axial hydrogen at C-3,[94] of the rates of quaternization of the base and related bases[86] and of the relationship of ajmaliciol and 19-isoajmaliciol (93) to 19-corynantheidone-20α (91) and -20β (92), the last-named being the more stable of the two epimeric ketones.[96]

Mitraphylline, isolated from *Mitragyna rubrostipulacea* Havil and from *M. stipulosa* Kuntze, has the composition $C_{21}H_{24}O_4N_2$ and contains one COOMe and one C—CH_3 group; the infrared spectrum indicates the presence of the system Ar—NH—CO— very probably as an oxindole unit, and the ultraviolet spectrum suggests that the system

MeOOC—C=CH—O—C

is present in the alkaloid as it is in ajmalicine.[85] Distillation of the hydrochloride with zinc dust yields isoquinoline, 3,4-diethylpyridine and a neutral substance $C_{10}H_9ON$, which has the spectra of an oxindole and can be reduced to 3-ethyloxindole, but which is stable to ozone. This compound may thus be formulated as spiro-3,3-cyclopropyloxindole (96)[58, 95] and this was confirmed by synthesis (94) → (96).[59, 66]

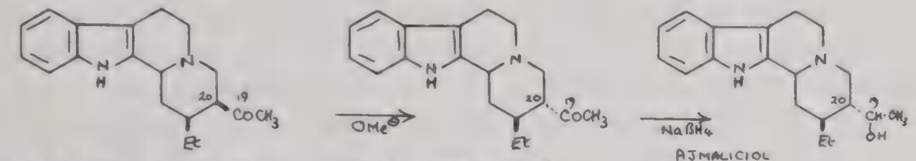
Dilute mineral acid converts mitraphylline into mitraphyllal ($C_{19}H_{24}O_3N_2$) which is a hemiacetal and no longer contains the carbomethoxy group, and Wolff–Kishner reduction of this gives mitraphyllane ($C_{19}H_{26}O_2N_2$). These reactions harmonize with the hypothesis that the base contains the system (97) which is transformed successively into (99) and (100).[85] Dehydrogenation of mitraphyllal gives 3,4-diethylpyridine and 3-ethyloxindole. Vigorous reduction of the base with lithium aluminium hydride affords dihydrodesoxymitraphyllol, which no longer shows carbonyl absorption and is in fact an aromatic amine,



(82) (90) (89)

(86) (87) (88)

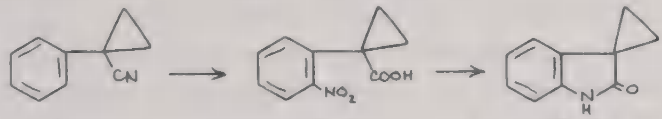
(85)



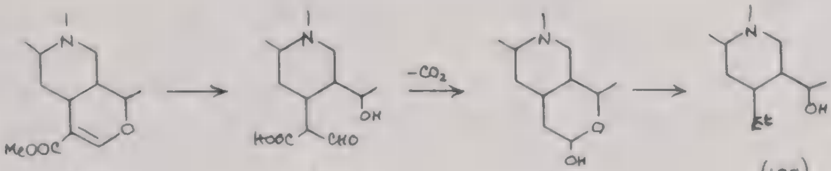
19-CORYNANTHEIDONE-20α
(91)

19-CORYNANTHEIDONE-20β
(92)

AJMALICIOL
19-ISOAJMALICIOL
(93)



(94) (95) (96)



(97) (98) (99) (100)

and the failure of this reduction to afford an indole indicates that in mitraphylline the oxindole system must be 3,3-disubstituted. Accordingly, since mitraphylline must be pentacyclic, the alkaloid may be assigned the structure (102) and dihydrodesoxymitraphyllol must be (101).[85]

The structure (102) for mitraphylline has been confirmed by conversion of ajmalicine (105) into the chloroindolenine (106) and the transformation of this, through the transient intermediates (107) and (108) into an equilibrium mixture of two oxindoles, mitraphylline (102) and isomitraphylline (104), which are in equilibrium through the ion (103). This process is a general one for conversion of indole alkaloids into their oxindole analogues.[37, 87]

The stereochemistry of mitraphylline and related oxindole alkaloids has been studied from the conformational angle by Hendrickson, who arrived at conclusions in agreement with structure (102).[48]

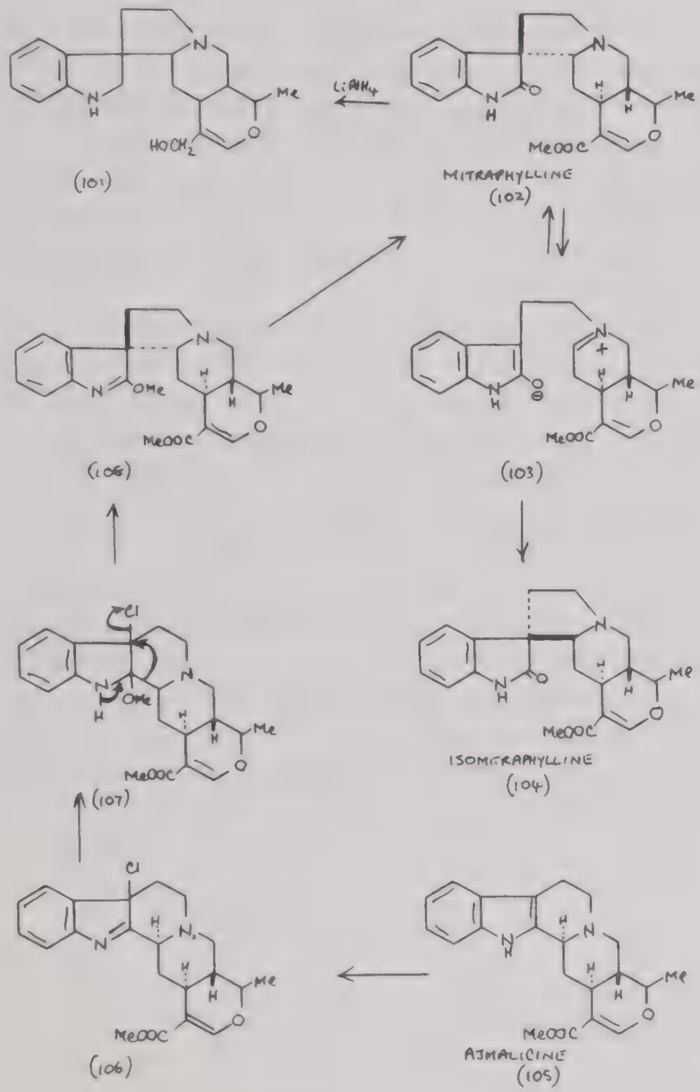
Akuammicine (109)

The seeds of *Picralima nitida* (stapf), Th. and H. Durand, which are used in West Africa as an antipyretic and antimalarial drug, contain a number of alkaloids of which akuammicine is one. The base has the composition $C_{20}H_{22}O_2N_2$ and contains the following systems revealed by infrared and ultraviolet spectra: a carbomethoxy group, a 1,2-disubstituted benzene ring, and a dihydroindole system conjugated with the ester group in some way. It contains in addition a reducible double bond which is unconjugated with the chromophoric system.

The carbomethoxy group is reduced by vigorous treatment with lithium aluminium hydride to $—CH_3$, which is unusual, and cautious acid hydrolysis is accompanied by decarboxylation, the product being a base of composition $C_{18}H_{20}N_2$. These two reactions and the ultraviolet absorption of the alkaloid are best accounted for by the assumption that the base contains the system

$$Ar—NH—C{=}C—COOMe$$

since this, being the vinylogue of a urethane, would be expected to suffer decarboxylation readily after hydrolysis. Lithium aluminium hydride reduction of such a system would initially afford an allylic alcohol, further reduction of which, by hydrogenolysis, to the *C*-methyl compound, would not be surprising.



(101)

MITRAPHYLLINE (102)

(103)

ISOMITRAPHYLLINE (104)

AJMALICINE (105)

(106)

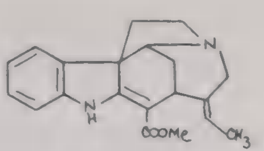
(107)

(108)

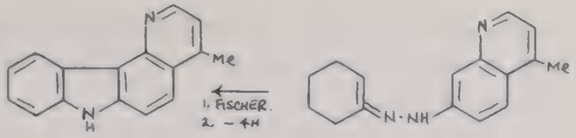
As the alkaloid gives β-ethylindole and β-methylindole on selenium dehydrogenation it is assigned to the β-indole series of bases and, as β-ethylpyridine is one product of zinc dust distillation, it has been given the structure (109). A further product of the selenium dehydrogenation is akuammicyrine, which has been assigned the structure (110); material of this structure has been synthesized from the base (111) but the identity of the two substances has not been rigorously established.[1]

The structure (109) for akuammicine was confirmed by Smith and his co-workers[89b] as follows. Reduction of the alkaloid with zinc and methanolic sulphuric acid resulted in saturation of the conjugated double bond to give dihydroakuammicine (109A), which was catalytically reduced to the tetrahydro base (109B), and this was epimerized to (109C) which in turn was prepared from the Wieland–Gumlich aldehyde (109D) as shown.

Smith and Wróbel[89a] earlier had uncovered a reaction of considerable structural significance in the relationships of certain alkaloids of the indole group. Akuammicine on hydrolysis in sealed tubes affords the indolenine base decarbomethoxyakuammicine (109E) which is presumably in reverse Mannich equilibrium with (109F), since on reduction with sodium borohydride it yields the indole base (109G), zinc dust distillation of which gives high yields of 3-ethylpyridine and 3-ethyl-2-methylindole. The relationship of (109F) to aspidospermatine (132) is obvious, since its transformation into (109H) followed by Mannich recyclization would give the correct skeleton. The same sort of Mannich equilibrium presumably relates the bases of the aspidospermine (199H) and quebrachamine (199K) groups or their precursors, from which also bases of the eburnamine (224) group are probably derived (see Chapter 10).

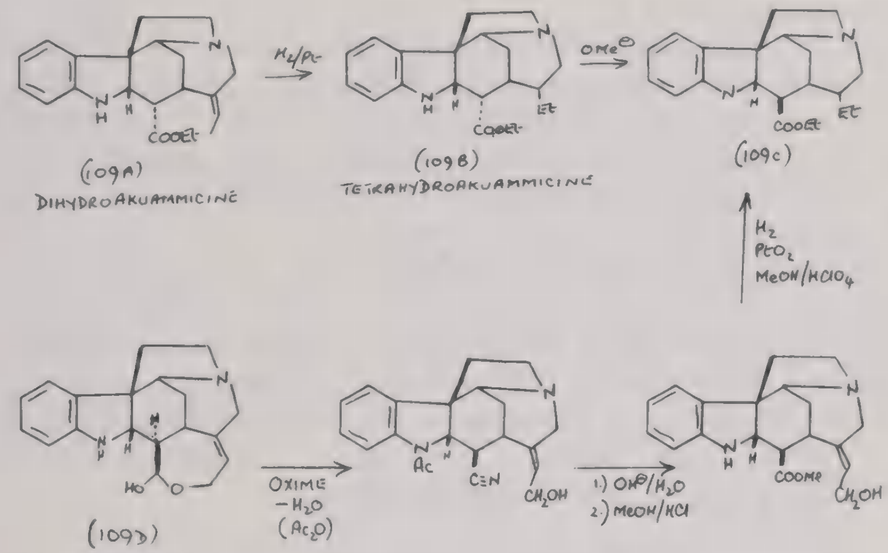


AKUAMMICINE
(109)



(110)

(111)



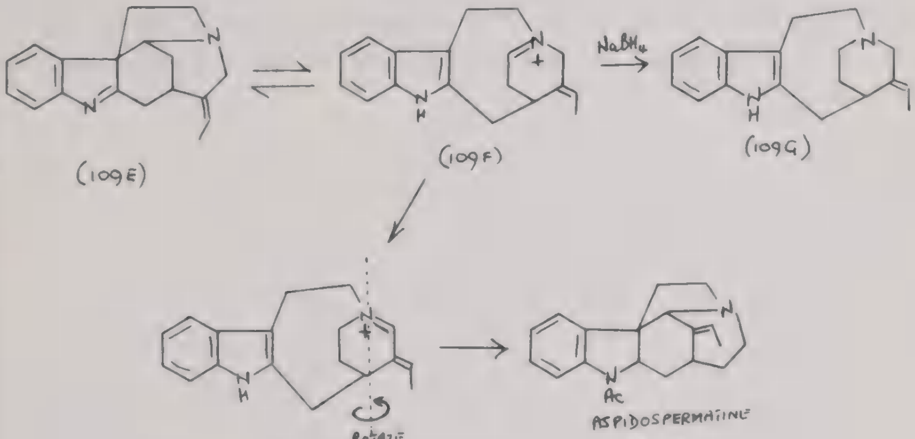
(109A)
DIHYDROAKUAMMICINE

(109B)
TETRAHYDROAKUAMMICINE

(109C)

(109D)

WIELAND-GUMLICH
ALDEHYDE



(109E)

(109F)

(109G)

(109H)

ASPIDOSPERMATINE
(132)

Akuammicine (109) with methanol at 80° gives the zwitterion (109K), which at 140° is converted into 3-ethylpyridine and 2-hydroxycarbazole (109M), presumably via (109L).[89c]

The alkaloid mossambine behaves as an analogue of akuammicine and has been shown by mass spectral studies to be 14-hydroxyakuammicine (see below under 'Condylocarpine').[68]

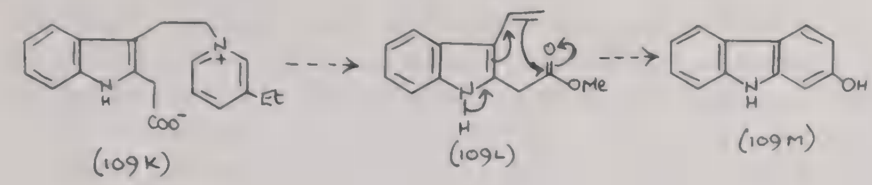
Geissospermine (123)

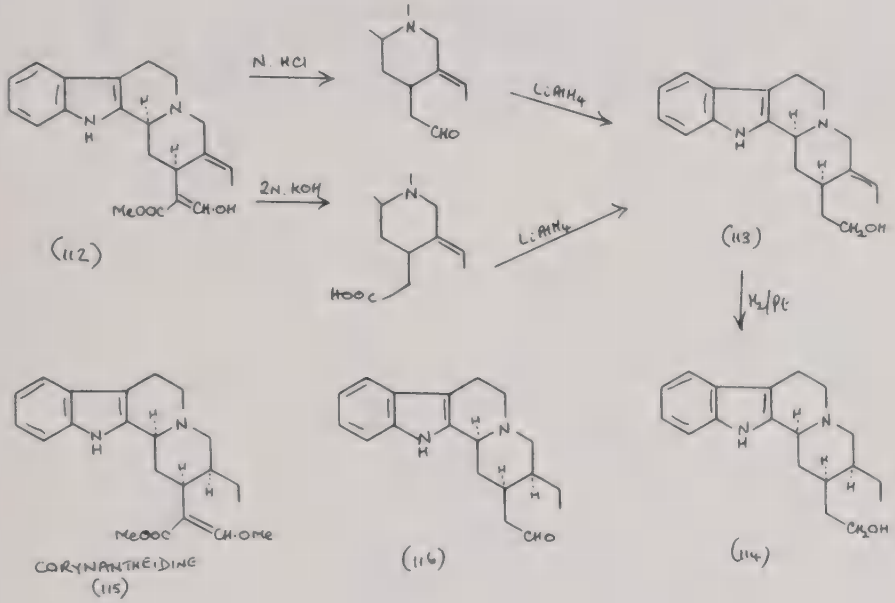
This is a bimolecular alkaloid containing an indole and a dihydroindole unit, obtainable from *Geissospermum laeve* (Vellozo) Baillon. It has the composition $C_{40}H_{48}O_3N_4$ and may be split by mineral acids into two bases, geissoschizine, $C_{21}H_{24}O_3N_2$, and geissoschizoline, $C_{19}H_{26}ON_2$, and from these two fragments the original alkaloid may be reconstituted by dissolution in 10% acetic acid.

Geissoschizine contains a $—COOCH_3$ group, a $—C—CH_3$ group (present as $C{=}CH—CH_3$ since ozonolysis of the base affords acetaldehyde) an aldehyde group and an indole chromophore. On dehydrogenation it affords alstyrine (75)[76] and some relationship to the ajmalicine type of structure is thus possible. The aldehyde group is present in a β-aldehydo–ester system, as is shown by hydrolysis experiments which afford both the related aldehyde and acid:

$$\mathrm{HOOC—CH_2—} \xleftarrow{2N\ \mathrm{KOH}} \mathrm{MeOOC—CH—CHO} \xrightarrow{N\ \mathrm{HCl}} \mathrm{—CH_2—CHO}$$

The structure (112) thus seems plausible for geissoschizine, and has been confirmed by conversion of the base into corynantheidol (114) also obtainable from the alkaloid coryantheidine (115) as shown opposite.[52, 77]


(109K)
(109L)
(109M)
COO⁻
Et
OMe
OH

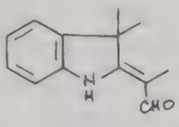

N. HCl
2N. KOH
LiAlH₄
LiAlH₄
H₂/Pt
CHO
HOOC
MeOOC
CH·OH
CH₂OH
CH·OMe
(112)
(113)
(114)
CORYNANTHEIDINE
(115)
(116)

Geissoschizoline, the second fission fragment, contains a CH_2OH and a C—Et group, and on zinc dust distillation affords 3-ethylpyridine. On Oppenauer oxidation it yields a base which has ultraviolet absorption corresponding to the chromophore (117) present in fluorocurarine[23, 57] suggesting the possible structure (118) for geissoschizoline which has been confirmed by partial synthesis from akuammicine (119) as shown opposite via the bases (120) and (121).[42, 53]

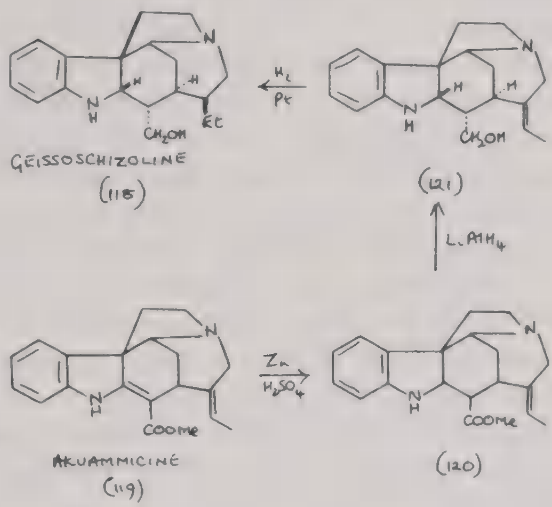
The absence in geissospermine of the chromophore

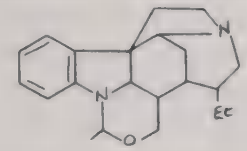
$$\mathrm{MeOCC{-}C{=}C{-}O}$$

characteristic of the enolized β-aldehydo-ester system of geissoschizine and of the free hydroxyl of geissoschizoline, and the ready condensation of the last named base with acetaldehyde to give the base (122) indicate that in geissospermine the two units are joined as in formula (123).[52]

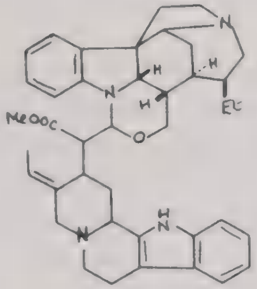


(117)





(122)



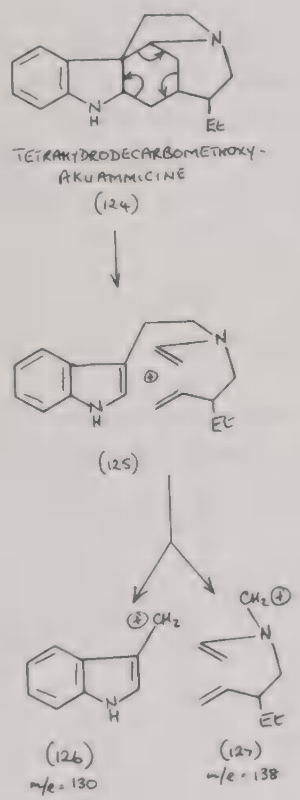
GEISSOSPERMINE

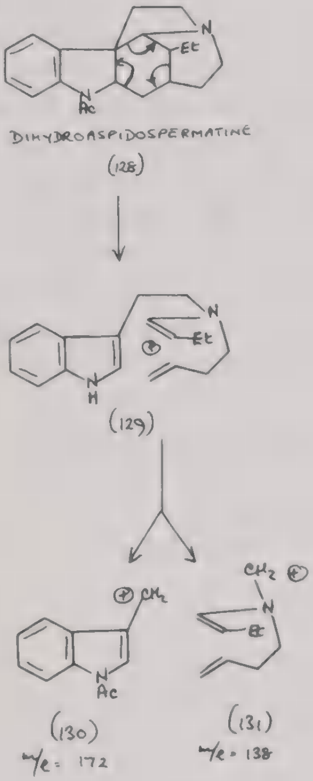
(123)

Aspidospermatine (132) and Condylocarpine (142)

Recently a group of alkaloids closely related to akuammicine and all having the same carbon skeleton was isolated from *Aspidosperma quebrachoblanco*.[28] All the bases of this group were shown by NMR studies to contain the system $C{=}CH{-}CH_3$ and the skeletal structure of aspidospermatine (132) was determined by examination of the mass spectrum of the base. This method of structure determination has recently been shown to be of great value in the natural product field, especially as it can be used with very small amounts of material. Briefly the method consists of the vapourization of a small amount of material in a high vacuum and bombardment of this with an electron beam of about 50–70 ev, under which conditions a molecular ion is formed by removal of one electron, and this ion may fragment or rearrange in various well defined ways, according to the structure of the parent compound. The ions are then accelerated and deflected by a magnetic field into a collector. The resulting spectrum of fragments frequently enables the structure of the parent compound to be deduced using a knowledge of the probable mode of fragmentation of the initial molecular ion. The theory and use of mass spectrometry has been well reviewed by Biemann.[26]

The fragmentation of compounds of the same carbon skeleton proceeds in the same way, the mass numbers of the fragments varying with the various substituents on those fragments. The ultraviolet spectrum of aspidospermatine is that of a dihydroindole, and *N*-deacetyldihydroaspidospermatine is isomeric with tetrahydrodecarbomethoxyakuammicine (124), but the spectra of the two bases are sufficiently different to rule out the possibility that they are diastereoisomers. The fragmentation patterns of the akuammicine derivative (124) and dihydroaspidospermatine in the mass spectrometer are also similar, allowing for the mass differences introduced by the *N*-acetyl group of the latter, and in particular both give a fragment with mass number 138. In the case of (124) this is regarded as arising by the fragmentation (124) → (125) → (126) + (127), and the fragment mass number 138 from dihydroaspidospermatine must be isomeric with (127). It is assigned the structure (131) since both aspidospermatine and akuammicine give β-ethylpyridine on zinc dust distillation.

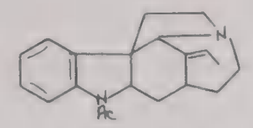

N
H
Et
TETRAHYDRODECARBOMETHOXY-AKUAMMICINE
(124)
(125)
⊕CH₂
CH₂⊕
(126)
m/e = 130
(127)
m/e = 138


N
Ac
Et
DIHYDROASPIDOSPERMATINE
(128)
(129)
⊕CH₂
CH₂⊕
(130)
m/e = 172
(131)
m/e = 138

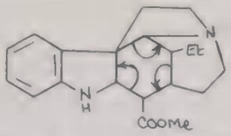
Assuming the same fragmentation pattern for (124) and dihydroaspidospermatine the latter is assigned the structure (128), fragmenting as shown, and aspidospermatine itself must be (132).[28] The same carbon skeleton has been demonstrated for condylocarpine from *Diplorrhynchus condylocarpon*, and structures have been assigned to further fragments detected in this case in the mass spectrometer. Condylocarpine is isomeric with akuammicine and the UV and IR spectra of the two bases are very similar. Clemmensen reduction of the alkaloid affords a base the mass spectrum of which shows a peak four mass units higher than that of condylocarpine which accordingly must contain two double bonds. The same mass spectrum shows peaks at mass numbers 295, 227, 144, 130, 196 and 158 which are logically accounted for by the fragments (135), (136), (137), (138), (139) and (140) derived via the initial product (134) from structure (133) for tetrahydrocondylocarpine. Had this last-named base had the ethyl group placed as in (124) fragments of mass numbers 295, 144, 130, 196 and 158 would still have been obtained, but that of mass number 227 would have been replaced by one of mass number 199 (141). Condylocarpine may thus be assigned the structure (142) (compare with akuammicine (109)); the reduction of the ethylidene group to ethyl during the Clemmensen reaction of the alkaloid is unusual and may be represented as in formulae (143) → (145).[27]

It may be noted that condylocarpine has, apart from the two-carbon bridge joining the indole system to the basic nitrogen atom, the same carbon skeleton as uleine (51).

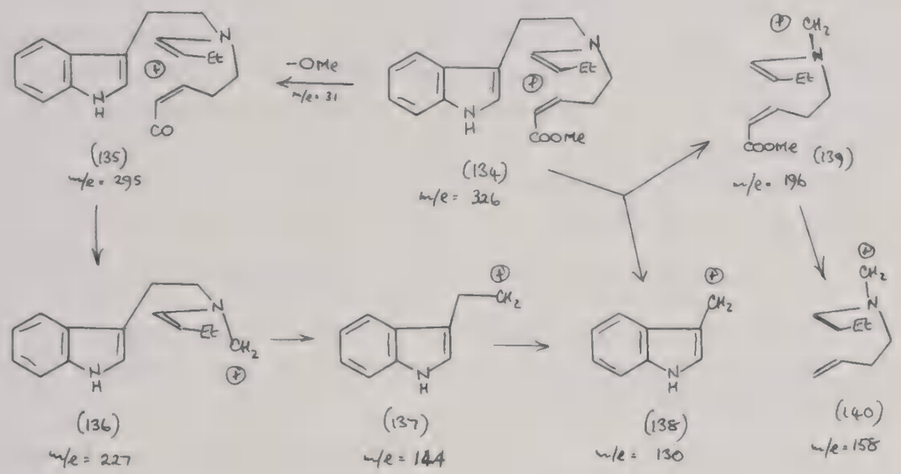
By methods analogous to those described above mossambine has been shown to be 14-hydroxyakuammicine (146),[68] the fragmentation of this base in the mass spectrometer following the same pattern as that of akuammicine.

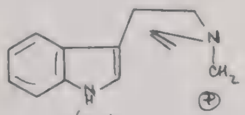


ASPIDOSPERMATINE
(132)

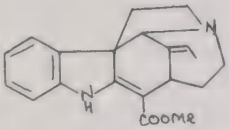


TETRAHYDROCONDYLOCARPINE
(133)

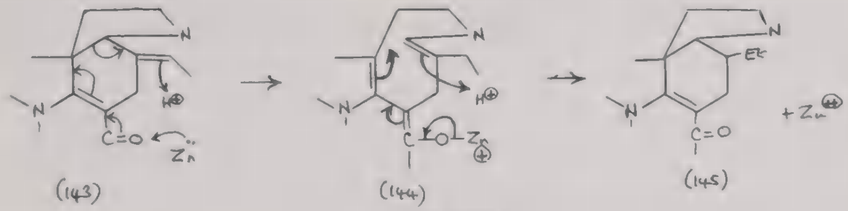


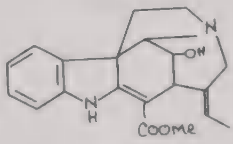


(141)
m/e = 199 NOT OBTAINED
FROM (133)



CONDYLOCARPINE
(142)





MOSSAMBINE
(146)

Ajmaline (158)

Ajmaline, one of the major alkaloids of *Rauwolfia serpentina* and other *Rauwolfia* species, has the composition $C_{20}H_{26}O_2N_2$ and contains one *N*-methyl, one *C*-methyl and two hydroxyl groups and a second tertiary nitrogen. Its ultraviolet spectrum is that of a dihydroindole and since it affords ind-*N*-methylharman (147) on soda-lime distillation it must contain the system (148).[79] Although the alkaloid contains two acetylatable hydroxyl groups it nevertheless possesses reducing properties and forms an oxime; this is due to the presence of a carbinolamine system, the presence of which is demonstrated by the following reactions:[3, 79]

(a) Huang-Minlon reduction gives dihydrodeoxyajmaline containing 2 C—CH_3 groups

$$>\text{N—CH(OH)—C}\leqq \;\longrightarrow\; >\text{NH}\ \ \text{CH}_3\text{—C}\leqq$$

(b) Sodium borohydride reduction gives a secondary base–primary alcohol, dihydroajmaline, convertible via the bromide into deoxyajmaline.

$$>\text{N—CH(OH)—C}\leqq \;\longrightarrow\; >\text{NH}\ \ \text{HOCH}_2\text{—C}\leqq \;\longrightarrow$$
$$>\text{NH}\ \ \text{BrCH}_2\text{—C}\leqq \;\longrightarrow\; >\text{N—CH}_2\text{—C}\leqq$$

(c) The methiodide behaves as the salt of a tertiary base and the corresponding base can be distilled, and shows carbonyl absorption at 5·80 μ.

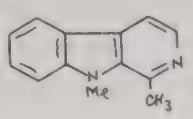
$$\overset{+}{>}\text{NMe—CH(OH)—C}\leqq \;\rightleftharpoons\; \overset{+}{>}\text{NHMe}\ \ \text{OHC—C}\leqq \;\xrightarrow{\text{OH}^-}$$
$$>\text{NMe}\ \ \text{OHC—C}\leqq$$

(d) The oxime can be converted into an aminonitrile (which gives ajmaline on reduction with lithium aluminium hydride) and an amino acid.

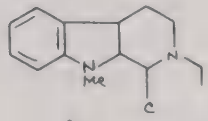
$$>\text{NH}\ \ \text{HON}=\text{CH—C}\leqq \;\longrightarrow\; >\text{NH}\ \ \text{N}\equiv\text{C—C}\leqq \;\longrightarrow$$
$$>\text{NH}\ \ \text{HOOC—C}\leqq$$

(e) Ajmaline can be decarbonylated by Raney nickel to decarbonoajmaline

$$>\text{N—CH(OH)—C}\leqq \;\longrightarrow\; >\text{NH}\ \ \text{HC}\leqq$$



(147)



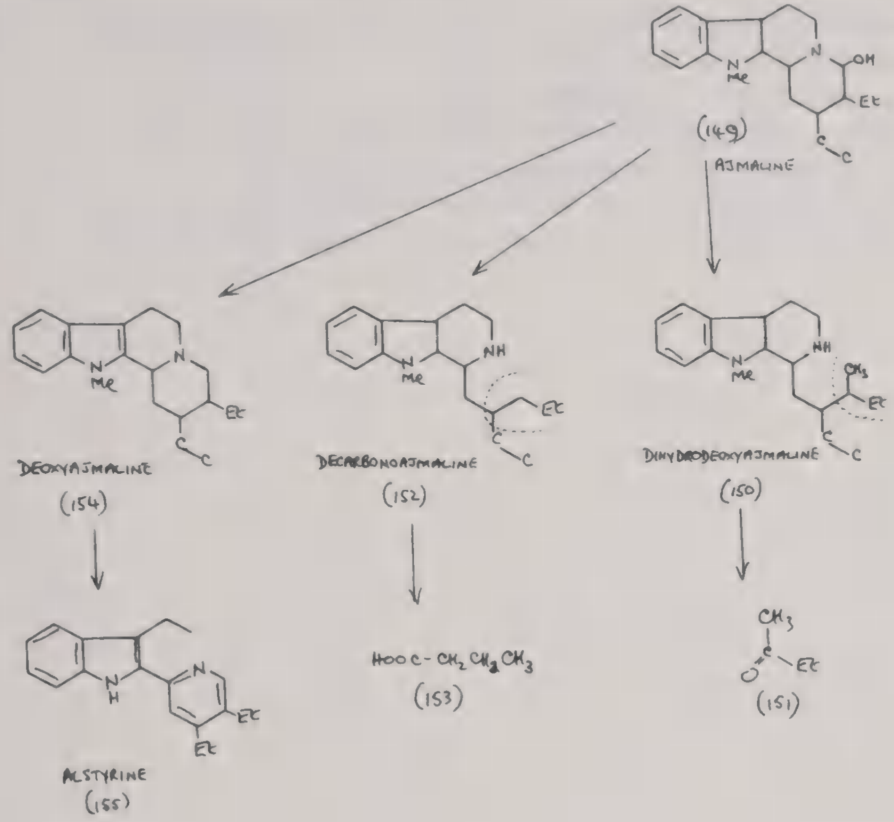
(148)

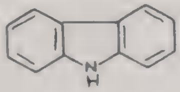
A number of reactions characteristic of carbinolamines are, however, not shown by ajmaline; for example it is not reduced by zinc and hydrochloric acid, it forms an *O*-acetyl derivative without fission of the N–C bond, and it fails to condense with acetone. These limitations are probably due to a bridgehead position for the nitrogen, prohibiting formation of the ammonium form

$$\geq\overset{+}{N}=CH\text{—}C\leq$$

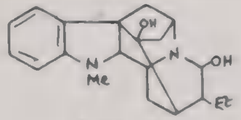
The further environment of the carbinolamine system in ajmaline is revealed, and the part structure (148) further extended to (149), by the observations that oxidation of dihydrodeoxyajmaline (150) gives ethylmethyl ketone (151)[3] and oxidation of decarbonoajmaline (152) gives n-butyric acid (153)[7,9] while selenium dehydrogenation of deoxyajmaline (154) yields alstyrine (155), the structure of which is known from the results of ozonolysis and hydrolysis to *o*-aminopropiophenone and 3,4-diethylpyridine-6-carboxylic acid,[36] as previously described in the discussion of the structure of ajmalicine.

As ajmaline contains no reducible double bonds it must be hexacyclic, and accordingly, the two-carbon chain adjacent to the ethyl group must be linked in two places to the main skeleton. Since carbazole (156) as well as ind-*N*-methylharman (147) is produced during the zinc dust distillation of ajmaline, one point of attachment of this chain was assumed to be the β-position of the indole ring, and structure (157) was advanced for the alkaloid.[3] The second hydroxyl group was placed as shown at a bridge-head to account for its general inertness, but it was later shown that this hydroxyl must be secondary since deoxyajmaline can be slowly oxidized to a ketone, deoxyajmalone, by the Oppenauer method, and this ketone has the carbonyl group in a five-membered ring as revealed by the infrared spectrum. Deoxyajmaline is also rapidly oxidized by lead tetraacetate to an indole containing an aldehyde group and must therefore contain a secondary


(149)
AJMALINE
DEOXYAJMALINE
(154)
DECARBONOAJMALINE
(152)
DIHYDRODEOXYAJMALINE
(150)
ALSTYRINE
(155)
HOOC-CH₂CH₂CH₃
(153)
(151)

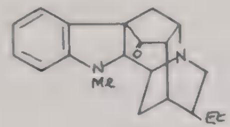


(156)

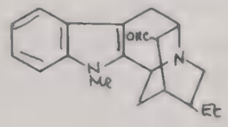


(157)

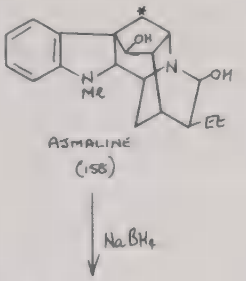
alcoholic group attached directly to the dihydroindole system. The structure (157) may thus be modified to (158), an alternative with the hydroxyl group at the position marked with an asterisk being much less plausible on biogenetic grounds.[78, 102] Deoxyajmalone thus becomes (159) and the aldehyde obtained from deoxyajmaline is (160). The structure (158) for ajmaline is further supported by the oxidation of dihydroajmaline (161) to the hemiacetal (162) which is readily further oxidized by silver oxide to a δ-lactone (163),[102] and by the



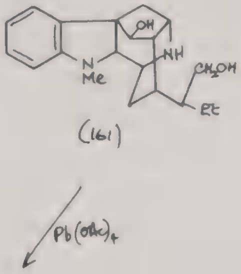
(159)



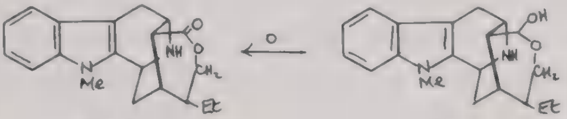
(160)



(158)



(161)



(163) (162)

dehydrogenation of dihydrodeoxyajmaline (164) to methylharman (165), ajarmine (166) and ajmyrine (167). The structures of these bases, whose origin from (164) is obvious, were established by synthesis, ajarmine by the route (168) → (170) → (166)[81] and ajmyrine by the route (172) → (176) → (167).[105]

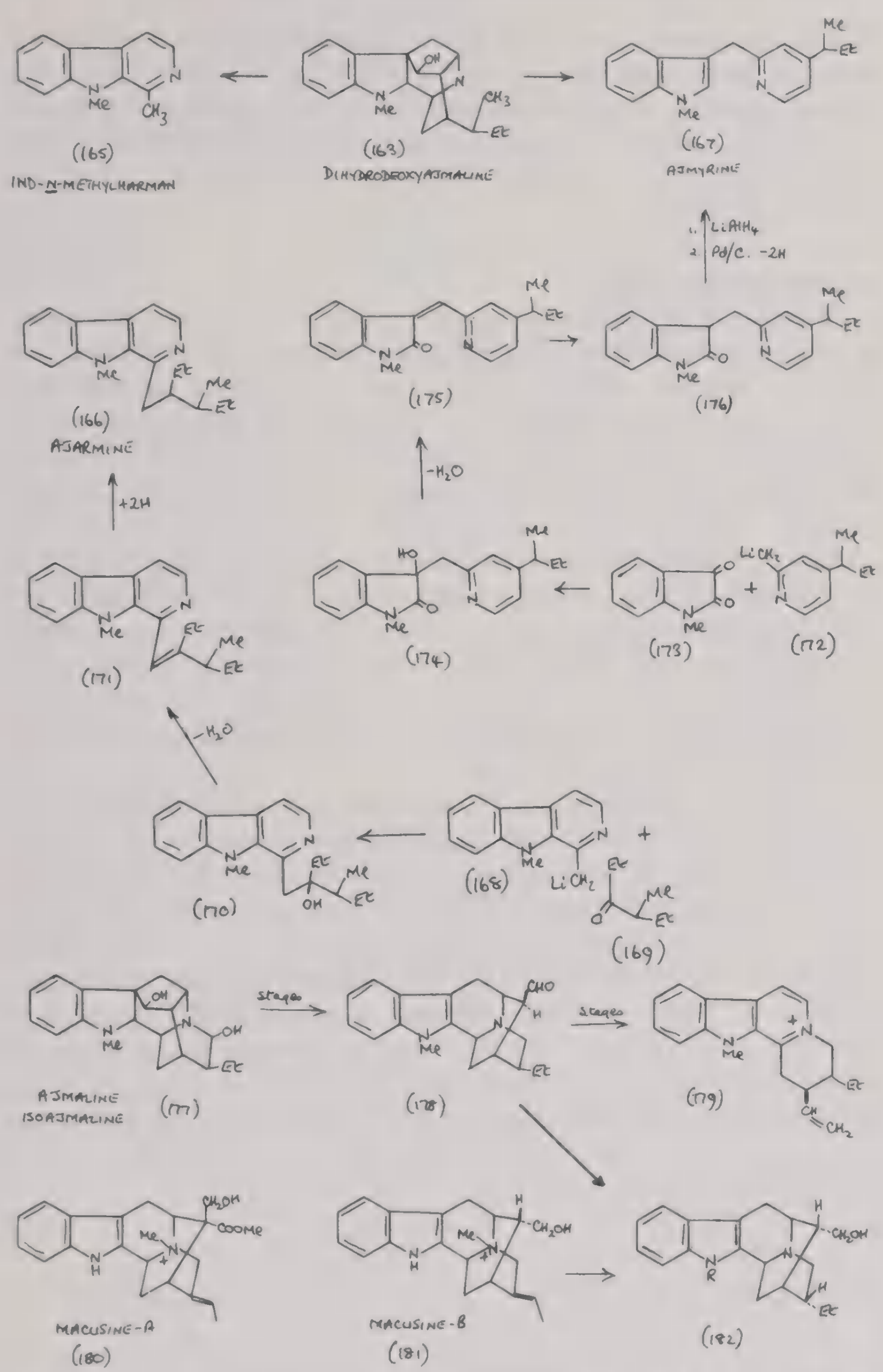
Isoajmaline, which can also be isolated from *Rauwolfia serpentina*, is stereoisomeric with ajmaline at the —CH.Et— group and can be obtained from ajmaline by the action of heat or alkali. It gives decarbonoajmaline on decarbonylation but affords dihydrodeoxyisoajmaline on Huang-Minlon reduction, indicating that the seat of isomerism is not the —N—CH(OH)— group.[3]

The stereochemistry of ajmaline and isoajmaline has been determined by conversion of the bases into the isomeric aldehydes (178), reduction to the alcohols, *O*-tosylation and boiling with collidine, when fission and aerial oxidation affords the quaternary salts (179) differing in orientation of the ethyl group.[12, 13]

Macusine-A, from *Strychnos toxifera*, has been shown by x-ray crystallographic studies to have the structure (180) and chemical evidence, not in itself sufficient to allow unambiguous assignment of structure, supports this view, e.g. selenium dehydrogenation appears to give alstyrine (155) and palladium dehydrogenation of the related tertiary base cannot be accomplished, which is indicative of the presence of a system in which simple aromatization is impossible.[63]

Macusine B, also isolated from *Strychnos toxifera*, has the closely related structure (181), since the related tertiary base dihydronormacusine-B (182, R = H) can be methylated to deoxyisoajmalol-B (182, R = Me), preparable from isoajmaline.[18]

Geissolosimine (*185*), the bimolecular alkaloid obtained from *Geissospermum vellosii*, is composed of an indole and a dihydroindole unit,

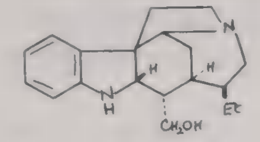

(165)
IND-N-METHYLHARMAN
(163)
DIHYDRODEOXYAJMALINE
(167)
AJMYRINE
1. LiAlH4
2. Pd/C. -2H
(166)
AJARMINE
+2H
(175)
(176)
-H2O
(171)
(174)
(173)
(172)
-H2O
(170)
(168)
(169)
stages
stages
AJMALINE
ISOAJMALINE
(177)
(178)
(179)
MACUSINE-A
(180)
MACUSINE-B
(181)
(182)

and like geissospermine may be split by mineral acid and reconstituted from the fission fragments by dissolving these in 1·5 *N* acetic acid. The fission fragments are geissoschizoline (183) and vellosimine, which is an aldehyde reducible to normacusine-B (184, $R=CH_2OH$) and must thus have the structure (184, $R=CHO$), and geissolosimine may be formulated as (185).[75]

Aspidospermine (188)

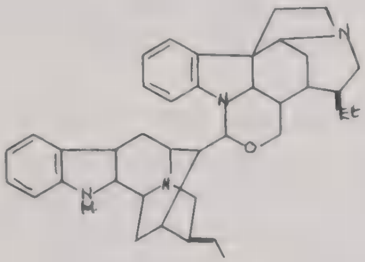
This base is the main alkaloid of *Aspidosperma Quebracho-blanco*. It has the composition $C_{22}H_{30}O_2N_2$ and contains one methoxyl, one —NAc— and one —C—CH_3 group and, since it does not contain a double bond, must be pentacyclic. The ultraviolet spectrum is that of a dihydroindole and a careful comparison of the spectrum with those of dihydroindole with methoxyl groups in each of the four available positions of the aromatic ring leads to the conclusion that the alkaloid contains the part structure (186). The C—CH_3 group must be present as —CH_2CH_3 since a modified Kuhn–Roth oxidation gives propionic acid. Comparison of the basicities of the two nitrogen atoms suggests that the relationship between the two is similar to that in strychnine, and as aspidospermine cannot be oxidized to an indole by mild oxidizing agents it must bear an aromatization-blocking substituent, probably at the β-position of the indole system.

Zinc dust distillation of the alkaloid leads to 3,5-diethylpyridine and 3-ethyl-5-methylpyridine[89] and the formation of the former of these led to the tentative advancement of structure (187) for the base.[101] However, Biemann[26] has recently found by mass spectral studies of the crude product, that the principal product (over 70%) in this degradation as well as in the zinc dust distillation of the related quebrachamine [29] (also previously reported to give 3,5-diethylpyridine[100]) is really 3-ethylpyridine. The structure of the base was finally shown by three-dimensional x-ray studies to be (188),[67] and the 3,5-disubstituted pyridines, which are only minor products of the zinc dust distillation



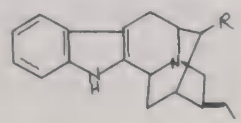
GEISSOSCHIZOLINE

(183)



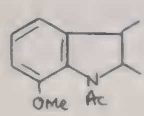
GEISSOLOSIMINE

(185)

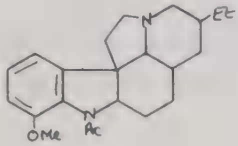


VELLOSIMINE R = CHO
NORMACUSINE-B R = CH_2OH

(184)



(186)



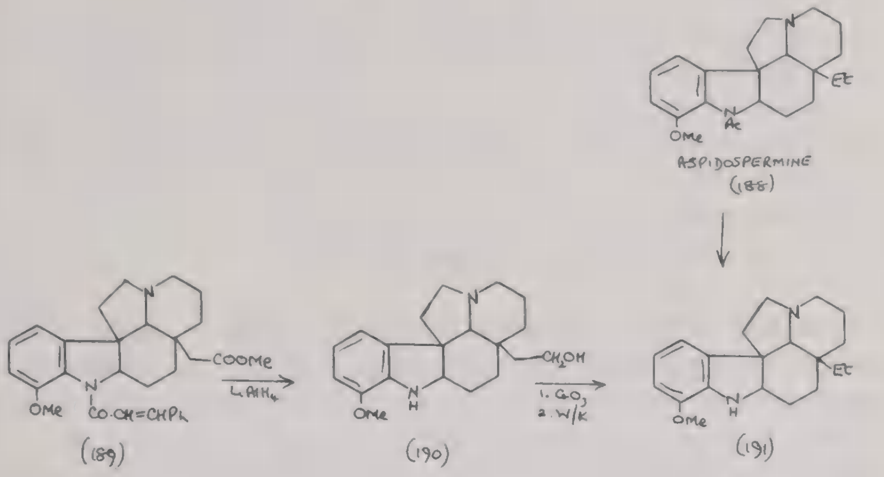
(187)

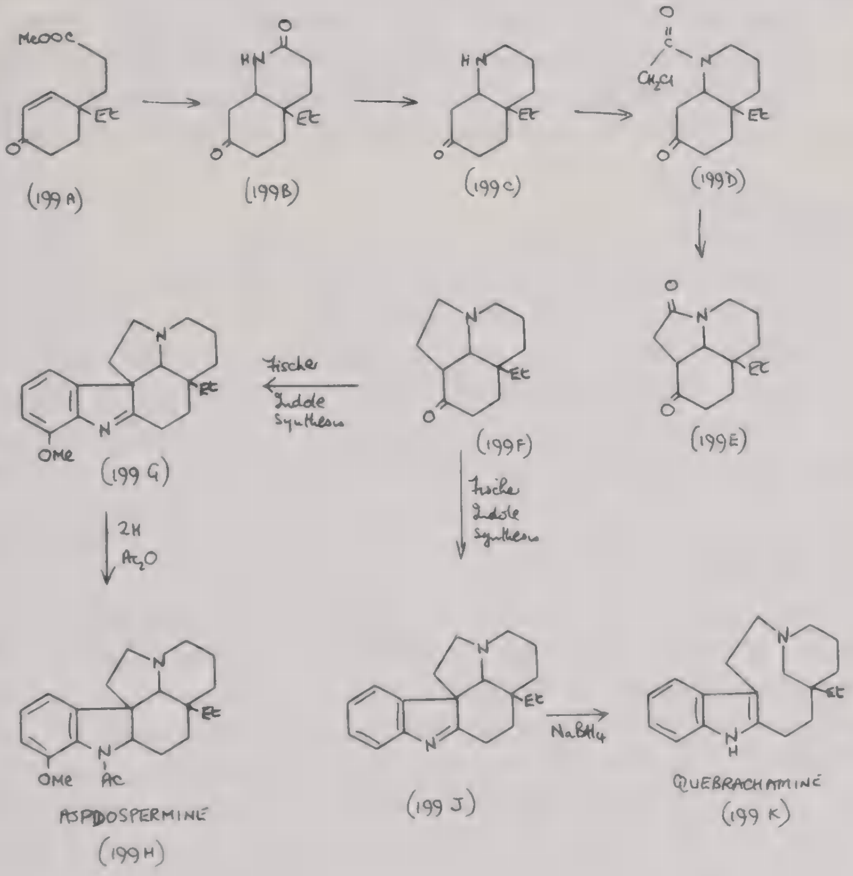
of the alkaloid, must arise by a migration of carbon atoms 1 and 2 of the hexahydrocarbazole system. A total synthesis of aspidospermine and quebrachamine has recently been reported,[89d] as shown in formulae (199A)–(199K).

A considerable number of analogues of aspidospermine are known, and the structures of these have largely been determined by NMR and mass spectral studies. The following may be mentioned.

Cylindrocarpine (189) NMR studies show the presence of a carbomethoxy group and acid hydrolysis affords methanol, cinnamic acid and cylindrocarpinic acid. Lithium aluminium hydride reduction gives dihydrocylindrocarpol (190), which on oxidation is converted into the corresponding aldehyde, and this in turn on Wolff–Kishner reduction yields deacetylaspidospermine, (191).[34]

Refractine (192) This alkaloid $C_{23}H_{28}O_4N_2$, contains an *ar*-methoxyl group, a carbomethoxy group and an N—CHO system, as shown by the NMR spectrum. Removal of the —CHO group by alkaline hydrolysis is accompanied by epimerization at the C—CH—COOMe asymmetric position. Mass spectrographic analysis reveals a fragmentation pattern


Et
OMe
Ac
ASPIDOSPERMINE
(188)
COOMe
LiAlH4
OMe
CO·CH=CHPh
(189)
CH2OH
1. CrO3
2. W/K
OMe
H
(190)
Et
OMe
H
(191)


MeOOC
Et
O
(199 A)
HN
O
Et
O
(199B)
HN
Et
O
(199C)
O
C
CH2Cl
N
Et
O
(199D)
O
N
Et
O
(199E)
N
Et
O
(199F)
Fischer
Indole
Synthesis
N
Et
OMe
(199 G)
2H
Ac2O
Fischer
Indole
Synthesis
N
Et
OMe
Ac
ASPIDOSPERMINE
(199H)
N
Et
(199 J)
NaBH4
N
Et
H
QUEBRACHAMINE
(199 K)

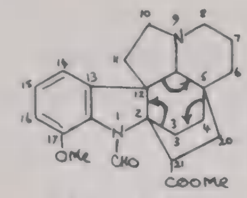
as shown by the arrows in (192) with loss of ethylene, a characteristic of the aspidospermine group, and further fragmentation of (193) to (194), m/e = 109. Lithium aluminium hydride reduction and *O*-acetylation of (192) affords the base (195) and this fragments to (196) which has m/e = 295 and (194), whereas use of lithium aluminium deuteride gives (195) with CD_2OAc which fragments to (196) with CD_2, having m/e = 297, and (194). The only possible points of attachment of the —COOMe group in (192) are thus C-21 and C-11, and the latter is regarded as very unlikely on biogenetic grounds.[35]

Pyrifoline (197) This base contains one —NAc— group and two methoxyl groups, one of which is aromatic and the other aliphatic. The ultraviolet spectrum is identical with that of aspidospermine, from which it may be concluded that the base is an *N*-acetyl-7-methoxydihydroindole. Mass spectral studies indicate a structure similar to those of aspidospermine and refractine, with a methoxyl group in the piperidine ring, and since the related ketone (199) exchanges only two hydrogen atoms for deuterium and the alcohol (198) is not a carbinolamine, structure (197) may be confidently assigned to the parent alkaloid.[38]

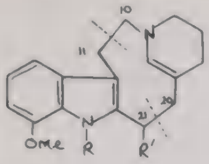
Ibogaine (205)

The root bark of the African shrub *Tabernanthe iboga* Baillon contains a number of closely related alkaloids of which the principal base is ibogaine. This has the composition $C_{20}H_{26}ON_2$ and contains one methoxyl one —NH— and one C—CH_3 group, no —NMe— group and no reducible double bond; its ultraviolet spectrum is closely similar to that of 5-methoxyindole, and since it gives 5-methoxy-*N*-oxalylanthranilic acid on permanganate oxidation it may be assumed to contain the system (200) and must be pentacyclic. The C—CH_3 group must be present in the alkaloid as CH_2—CH_3 since modified Kuhn–Roth oxidation affords propionic acid.

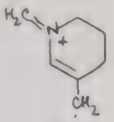
Alkali fusion of the alkaloid yields the indole (201) and the base (202)[42, 83] and selenium dehydrogenation affords the base (203) (the desmethoxy analogue of which, prepared in the same way from ibogamine, has been synthesized), together with a base that is formulated as (204), since it has the UV spectrum of a 2-*o*-aminophenylindole, contains two C—CH_3 groups and bears a secondary nitrogen in a hindered position (N—Ac difficult to hydrolyse).[91] These facts receive a ready



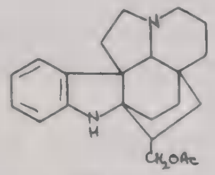
REFRACTINE
(192)



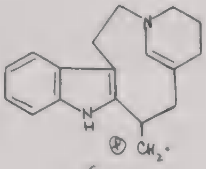
(193)



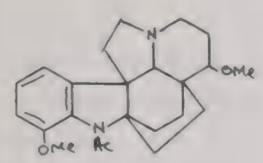
(194)
m/e = 109



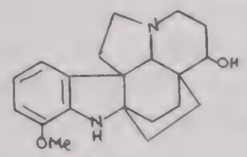
(195)



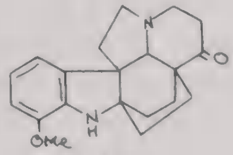
(196)



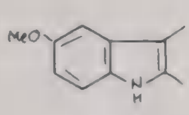
PYRIFOLINE
(197)



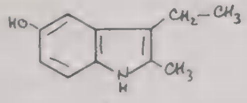
(198)



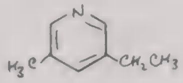
(199)



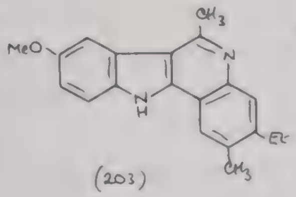
(200)



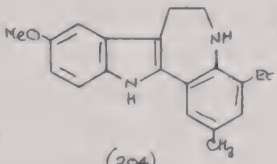
(201)



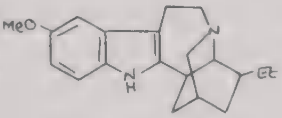
(202)



(203)



(204)



(205)
IBOGAINE

explanation on the basis of the structure (205) for ibogaine; fission of CH_2—N$\lessdot$ and aromatization gives (204) and ring-contraction and further dehydrogenation of this base leads to (203).[91] This structure for the alkaloid has been confirmed by x-ray studies.[54]

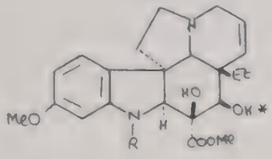
Leurocristine (209, R = CHO) and Vincaleucoblastine (200, R = Me)

These two closely related bases from *Vinca* species have created interest on account of their apparent oncolytic activity in experimental and human neoplasms,[50, 55, 93] and because they consist of two indole units one belonging to the aspidospermine group and the other to the ibogaine group.

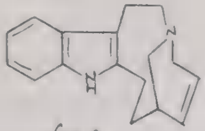
NMR spectral studies of vincaleucoblastine, $C_{46}H_{56}O_9N_2$, reveal the presence of the following: two different COOMe groups, one aromatic OMe, one OAc, one NMe, one NH present in an indole system, one tertiary free hydroxyl group and one hydrogen-bonded hydroxyl group. Leurocristine is shown by spectral studies to contain N—CHO in place of the NMe of vincaleucoblastine, and lithium aluminium hydride reduction of both bases affords the same pentahydroxy compound.

Cleavage of the alkaloids with acid affords in each case two bases, vincaleucoblastine gives desacetylvindoline (206, R = Me) and leurocristine gives des-*N*-methyldesacetylvindoline (206, R = H), the second product in each case being velbenamine, $C_{19}H_{26}ON_2$.[70] Desacetylvindoline is obtainable from the alkaloid vindoline by mild hydrolysis[40] and vindoline has been shown by NMR and mass spectral studies to have the structure (206, R = Me) acetylated on the asterisked hydroxyl.[39] Velbenamine, the second product of acid cleavage of the bases, appears to be a hydroxydihydro derivative of cleavamine (207), which is obtainable from the ibogaine-type alkaloid catharanthine (208) by the same acid treatment.[69]

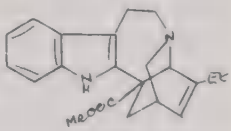
Comparison of the NMR spectra of vincaleucoblastine and leurocristine with those of the acid cleavage products reveals that in the bimolecular bases the absorption pattern of the vindoline sections shows the presence of only two aromatic protons in the 1,4-relationship and accordingly vincaleucoblastine is formulated as (209, R = Me) and leurocristine as (209, R = CHO). On biogenetic grounds and to account for the acid cleavage, the vindoline and hydroxyl groups are regarded as being at C-3/C-4 of the ibogaine-like unit.[70]



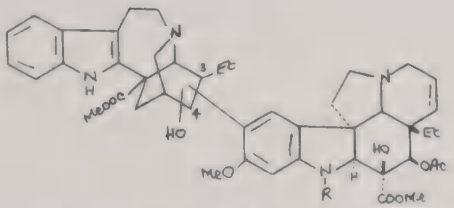
(206)



(207)



(208)



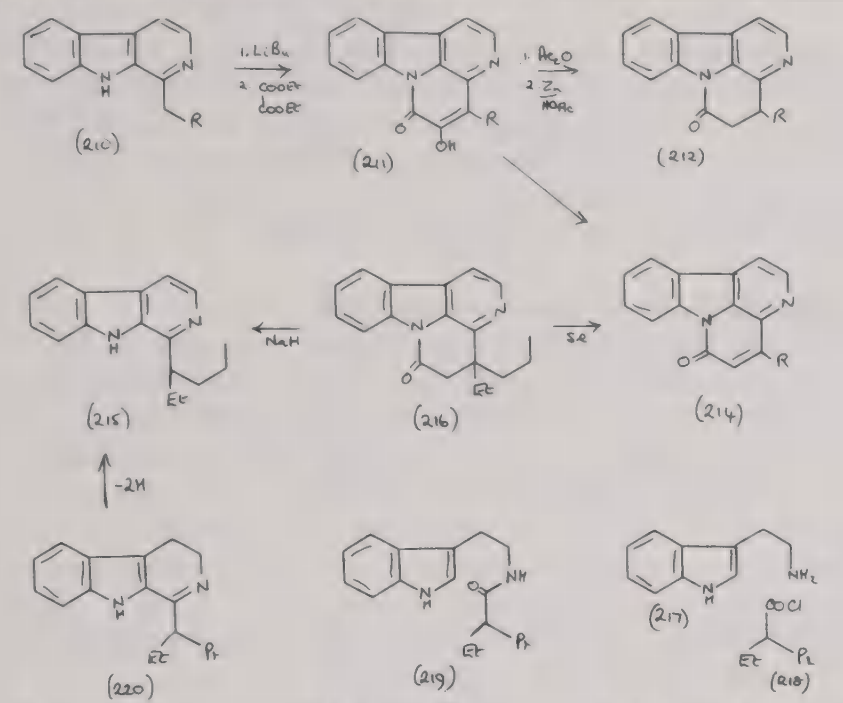
R= Me VINCALEUCOBLASTINE
R= CHO LEUROCRISTINE
(209)

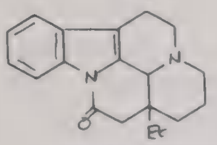
The Alkaloids of *Hunteria Eburnea*

Three closely related bases, eburnamonine, eburnamine and eburnamenine, have been isolated, among others, from *Hunteria eburnea*; eburnamonine is an *N*-acylindole and is obtainable by the oxidation of the carbinolamine eburnamine, which on dehydration also yields the third of these alkaloids, eburnamenine.

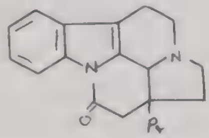
Eburnamonine, $C_{19}H_{22}ON_2$, has the ultraviolet spectrum of an *N*-acylindole and contains one $C—CH_3$ group, which must be present as $CH_2—CH_3$ since modified Kuhn–Roth oxidation affords propionic acid. Selenium dehydrogenation of the base affords a primary product which on further prolonged heating with selenium gives a mixture of 4-ethyl- and 4-propylcanthin-6-one (214, R = Et) and (214, R = Pr) both of which have been synthesized by the route (210) → (214). The primary dehydrogenation product may also be degraded by vigorous treatment with sodium hydride to the base (215), synthesized as shown from (218) via (220), and accordingly the primary product may be assigned the structure (216). These results lead to the possible formulae (221), (222) and (223) for eburnamonine, though the last two of these do not accord so well with the results of Kuhn–Roth oxidation.

Of these possible structures, (221) was shown to be correct by Wolff–Kishner reduction of the related eburnamine (224), which appears to react in this instance as the aldehyde (225), to the base (226); this was racemized via the quaternary salt (227) and the racemate was synthesized as shown opposite, from the base (228) via the amide (230).

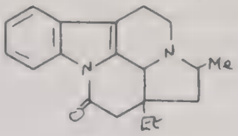




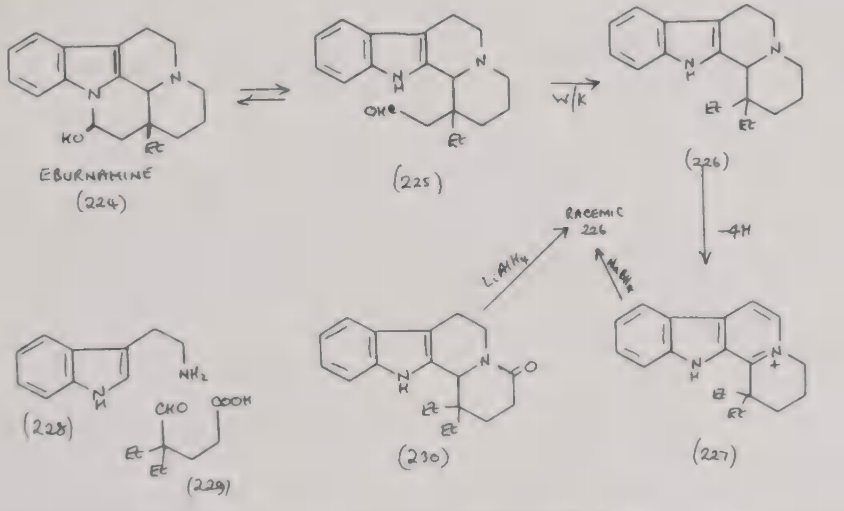
EBURNAMONINE
(221)



(222)



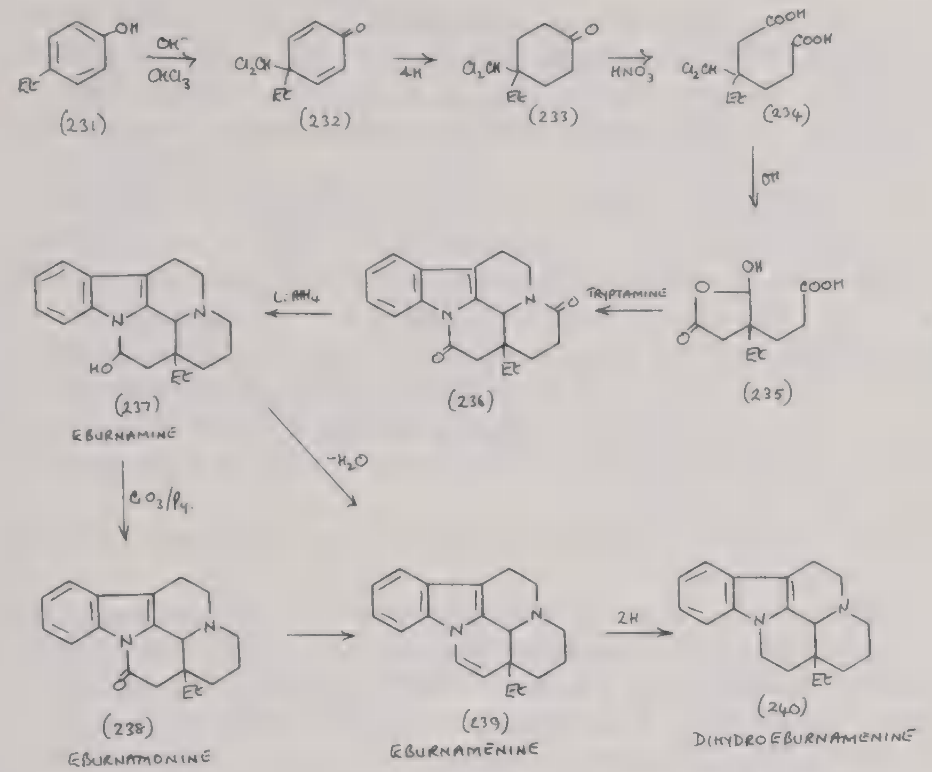
(223)



(±)-Eburnamonine has been synthesized as shown in formulae (231) → (238). The lithium aluminium hydride reduction of the intermediate (236) affords (±)-eburnamine (237), its epimer and dihydroeburnamenine (20), also obtainable from eburnamenine (239), and, since eburnamenine is preparable from eburnamine, syntheses of the racemic forms of all three alkaloids have been achieved.[14]

Calycanthine (252) and Chimonanthine (248)

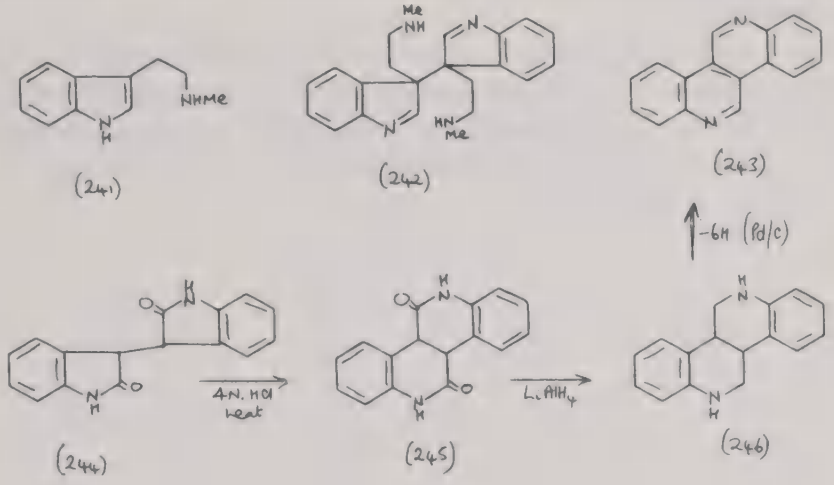
These two bases are closely related, both being derived from two units of tryptamine linked oxidatively. Calycanthine may be isolated from *Calycanthus glaucus* and also from the unrelated *Meratia praecox* (*Chimonanthus fragrans*) and its occurrence in two unrelated species argues a relatively simple mode of biogenesis. The structure of the base was finally worked out from biogenetic hypotheses. It has the composition $C_{22}H_{26}N_4$ and on pyrolysis it gives high yields of *N*-methyltryptamine (241) together with calycanine, $C_{16}H_{10}N_2$, also obtained by selenium dehydrogenation, which process also gives rise to β-carboline, 3-methylindole, 3-ethylindole and lepidine.[11] On the assumption that the parent alkaloid is derived from a β,β′-di-*N*-methyltryptamine (242)[80, 104] calycanine, which can be shown to contain a centre of symmetry, was formulated as (243), obtainable from a structure such as (242) by elimination of the angular substituents and relatively slight skeletal rearrangement, and this structure was proved correct by the synthesis of calycanine from leucoisoindigo (244) via (246) as shown opposite.[104]



(231) (232) (233) (234)

(237) EBURNAMINE (236) (235)

(238) EBURNAMONINE (239) EBURNAMENINE (240) DIHYDROEBURNAMENINE



(241) (242) (243)

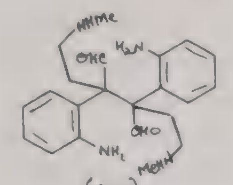
(244) (245) (246)

It was then assumed that calycanthine is a di-(*N*-acetal) of the dialdehyde (247) derived by the hydrolysis of (242), and of the possible structures (248)–(252) the one with greatest stability on steric grounds is preferred for the alkaloid on account of its stability in acids, and this form is (252), which can have all the rings in the chair or near-chair conformation as shown in (253). This assignment of structure is supported by the fact that oxidation of the alkaloid with mercuric acetate leads to dehydrocalycanthine, which must have the enamine structure (254) since it may be hydrolysed by alcoholic potash to methylamine and the amide-alcohol (255). Bases of structure (248)–(251) would be expected to be oxidized to amidines, and only in the case of (252) is amidine formation precluded by steric factors—the related amidine would have a double bond at a bridge-head, which is contrary to Bredt's rule.[104]

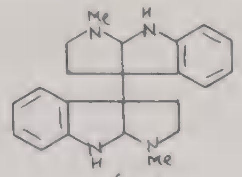
The structure (252) for calycanthine has been confirmed by x-ray diffraction studies.[47]

Chimonanthine, isomeric with calycanthine, is also obtained from *Meratia praecox* (*Chimonanthus fragrans*) and is closely related to the base folicanthine which is in fact its bis-*N*(a)-dimethyl derivative. Hofmann degradation of folicanthine dimethiodide affords the base (256), indicating that chimonathine probably has the structure (248) or (249),[51] and x-ray studies have clearly shown that (248) is the correct representation.[45]

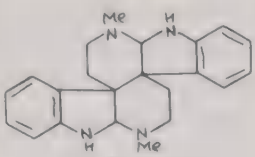
The various bases of the calycanthaceous alkaloid group are theoretically derivable by cyclization of the tetraaminodialdehyde (247), and the indolenine (257A) would be expected to yield chimonanthine directly under conditions unfavourable to hydrolytic cleavage of the



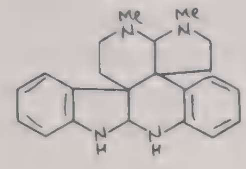
(247)



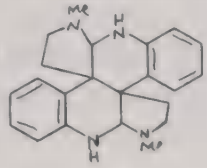
(248)



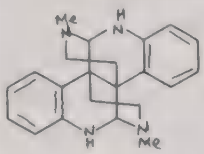
(249)



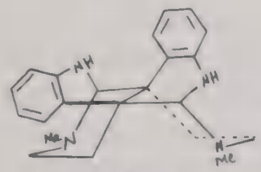
(250)



(251)



(252)



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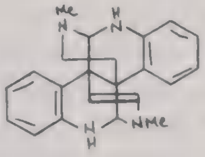

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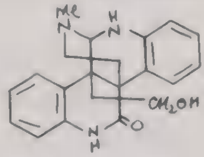
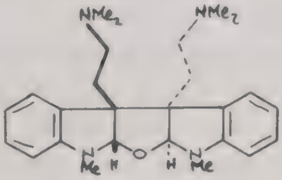


(255)



(256)

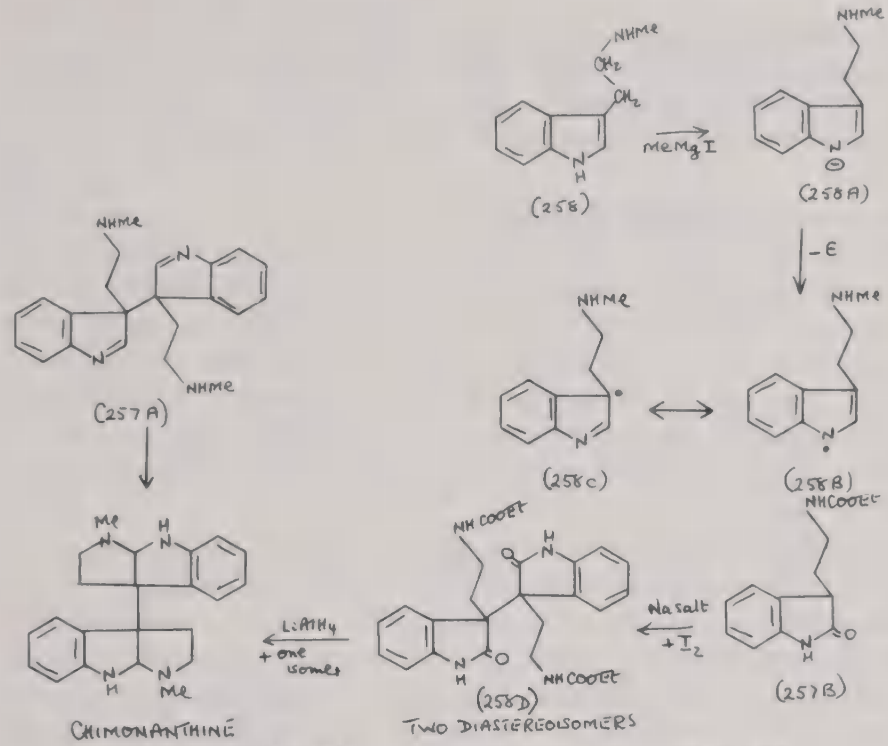
indolenine system; and Scott and his co-workers have recently reported[84a] a most elegant single-step synthesis of the alkaloid by the oxidation of the anion (258A) obtained by the action of methylmagnesium iodide on the indole (258). Ferric chloride oxidation of (258A) gives, by a one-electron transfer process, the radical (258B) $\longleftrightarrow$ (258C), dimerization of which yields (257A), and under the conditions of the reaction this cyclises to chimonanthine.

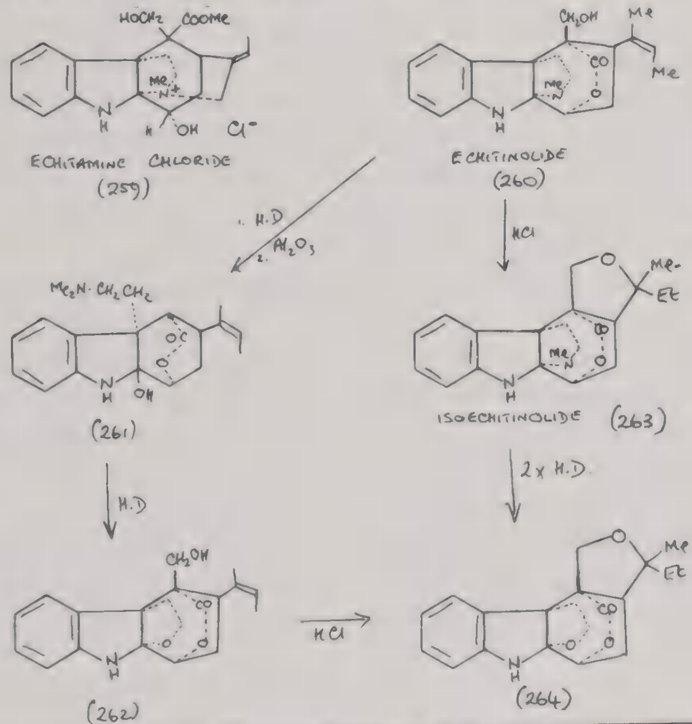
A synthesis of *meso*-chimonanthine less relevant to the probable biogenetic processes than this extremely simple indole dimerization, from the oxindole (257B) via the amide (258D) has been recorded.[49]

The alkaloid hodgkinsine[2] probably belongs to the calycanthaceous group, but its structure is more complex than those of known bases and awaits full elucidation.

Echitamine Chloride (259)

Echitamine chloride $C_{22}H_{29}O_4N_2Cl$ may be isolated from a number of *Alstonia* species. It is a quaternary chloride and contains in addition to the quaternary nitrogen the following groups: NH, OH primary and OH secondary, MeOOC and C=CH—CH_3 (giving acetaldehyde on ozonolysis). Careful study of the ultraviolet absorption of echitamine chloride and of echitinolide (the product of catalytic reduction) in neutral and acid solutions led to the conclusion that the alkaloid contains the system Ar—NH—C—N, but examination of the degradations of the compound failed to lead to any tenable proposals for its structure. The structures of echitamine chloride (259) and of the related bromide and iodide were finally elucidated by x-ray crystallographic studies,[46] and only subsequently was it possible to rationalize the reactions set out opposite in formulae (260)–(264).[30, 44]


NHMe
CH2
CH2
N
H
MeMgI
(258)
NHMe
N
⊖
(258A)
–E
NHMe
(258C)
NHMe
(258B)
NHMe
N
NHMe
(257A)
Me
N
H
N
N
H
N
Me
CHIMONANTHINE
LiAlH4
+ one isomer
NH COOEt
H
N
O
N
H
O
NH COOEt
(258D)
TWO DIASTEREOISOMERS
Na salt
+ I2
NHCOOEt
N
H
O
(257B)


HOCH2
COOMe
Me
N+
N
H
H
OH
Cl⁻
ECHITAMINE CHLORIDE
(259)
CH2OH
Me
CO
Me
N
O
Me
N
H
ECHITINOLIDE
(260)
1. H.D
2. Al2O3
Me2N·CH2CH2
OC
O
N
H
OH
(261)
HCl
O
Me
Et
O
Me
N
O
N
H
ISOECHITINOLIDE
(263)
H.D
2 x H.D
CH2OH
CO
O
O
N
H
(262)
HCl
O
Me
Et
CO
O
O
N
H
(264)

Echitamine chloride reacts with alkali to give echitamine base, probably (265); its ultraviolet absorption indicates that the system Ar—N—C—N is not present. The conversion of the base back into the salt by acids could proceed via the indolenine (266).[30]

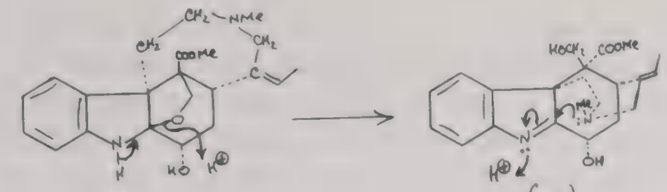
The Calabash Curare Alkaloids

Of the three types of curare (tube, pot and calabash) calabash curare yields the alkaloids of highest biological activity. These are the C_{40} quaternary salts such as toxiferine-I chloride related to C_{38} bases. These compounds contain two identical dihydro-indole units symmetrically linked. The bimolecular nature of these bases was first conclusively demonstrated by the fact that they can be partially quaternized to give compounds containing one quaternary and one tertiary nitrogen outside the indole residues.[74]

To illustrate the derivation of typical structures in this group we may take the compounds toxiferine-I chloride and caracurine-V and certain related alkaloids all obtainable from curare. Caracurine-V is unstable to acids and is rapidly converted by dilute sulphuric acid into caracurine-Va and finally into a mixture of caracurine-VII and caracurine-II, the production of the last of these requiring atmospheric oxygen. Caracurine-II can be methylated to the quaternary methochloride, which is also obtainable from toxiferine-I chloride by the action of aqueous acid and oxygen, and indeed toxiferine-I chloride can be obtained by the *N*-methylation of caracurine-Va. Also caracurine-VII, which is a C_{19} base, can be *N*-methylated to *C*-Alkaloid-A8, which yields toxiferine-I when kept in dilute acetic acid.[9, 16] The relationships are summarized on the opposite page.

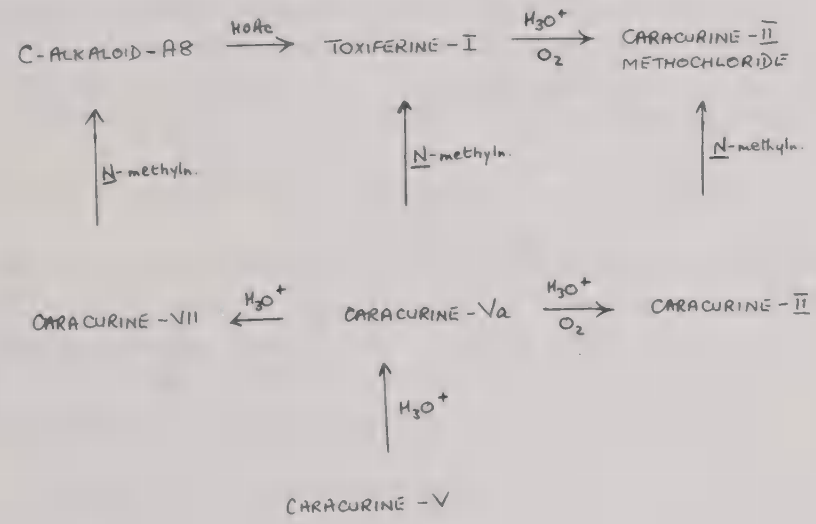
The whole process of structural analysis was greatly advanced by the discovery[24] that caracurine-VII is identical with the Wieland-Gumlich aldehyde (267), a well-known degradation product of strychnine;[88] *C*-alkaloid-A8 thus has the structure (268) and, as this salt is obtained by the fission of toxiferine-I, it has been given the name hemitoxiferine-I.

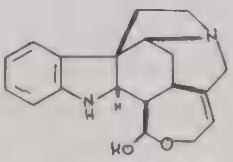
Another alkaloid isolated from calabash curare is a close relative of toxiferine-I and was originally erroneously named *C*-dihydrotoxiferine-I before the precise relationship between the two was known;[97]



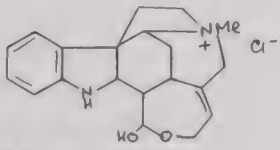
(265)

(266)





WIELAND-GUMLICH ALDEHYDE
CARACURINE-VII
(267)



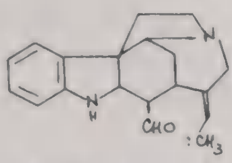
C-ALKALOID A-8
HEMITOXIFERINE-I
(268)

the correct name should be deoxytoxiferine-I. This alkaloid, like toxiferine-I, can be split by acids to 'hemidihydrotoxiferine-I' which is the aldehyde (269).[25] The chromophoric system of toxiferine-I and '*C*-dihydrotoxiferine-I' is Ar—N—C=C, and, assuming that this is present in a methyleneindoline group, the only way in which this can arise, by the union of two molecules of structure (269) with the simultaneous loss of two molecules of water and the disappearance of the hydrogen atoms attached to the dihydroindole nitrogen atoms, is by union to give (270), and this structure was first suggested for '*C*-dihydrotoxiferine-I'.[25] This structure has, however, been slightly modified to (271)[31] following a study of the nuclear magnetic resonance spectrum of the alkaloid, and the revised structure is in accord with the degradation of 'bisnor-*C*-dihydrotoxiferine-I' (the bistertiary base corresponding to (271)) to strychanone (272) by reduction of the two ethylidene groups and ozonolysis.[4]

On this basis the structure analogous to (270) originally proposed for toxiferine-I[16, 23] may be modified to (273).

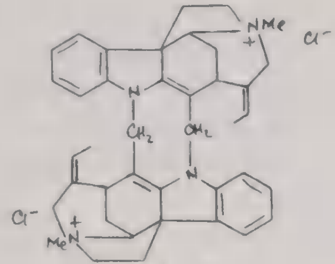
Caracurine-Va is the bistertiary base corresponding to (273) and is formed from caracurine-V by isomerization in acid solution. Caracurine-V does not contain the Ar—N—C=C chromophore, nor does it contain hydroxyl groups, and it may accordingly be assigned the aminohemiacetal structure (274).[23] Dimerization of the Wieland–Gumlich aldehyde (267) to caracurine-V in good yield may be achieved in buffered acetic acid[25] or in pivalic acid.[16] The corresponding methochloride (268) in acetic acid[16, 22] gives 20% of toxiferine-I and some caracurine-V dimethochloride, but mainly *O*,*O*-diacetyltoxiferine-I; whereas in pivalic acid, in which there is a strong steric hindrance to acylation, at least 70% of toxiferine-I is obtained,[16] and it is evident that the factors governing the possible cyclizations are finely balanced.

Caracurine-II is obtained by the treatment of caracurine-V with acid[9] and the corresponding bismethochloride is obtainable in the same way from toxiferine-I,[16] in both reactions the presence of oxygen being essential. Caracurine-II is stable to *N*-hydrochloric acid and glacial acetic acid at 120°, whereas caracurine-V and toxiferine-I under these conditions are split to caracurine-VII (267) and hemitoxiferine-I (267). Curacurine-II has the composition $C_{38}H_{38}O_2N_4$ (i.e. two hydrogen atoms less than caracurine-V) and, as it only contains two reducible double

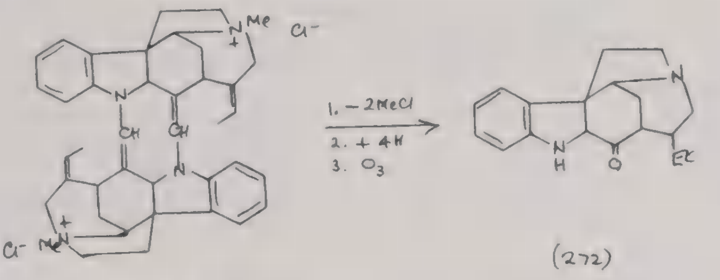


HEMIDIHYDROTOXIFERINE-I

(269)



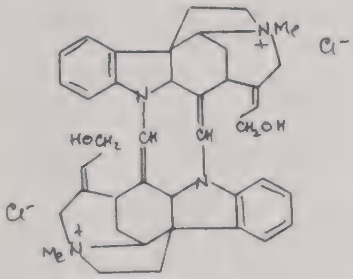
(270)



C-DIHYDROTOXIFERINE-I

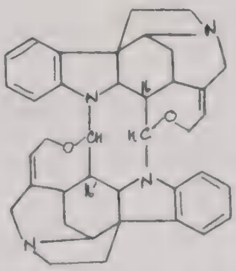
(271)

(272)



TOXIFERINE-I

(273)



CARACURINE-V

(274)

bonds, it must contain fourteen rings, one more than caracurine-V.[17] A study of the NMR spectrum of the alkaloid indicates[19] that the new carbon–carbon bond is between positions 16 and 16′. The structure (275) may thus be assigned to caracurine-II and this has been independently deduced from x-ray crystallographic studies of caracurine-II dimethiodide.[64]

A recent review of the calabash curare alkaloids is available.[15]

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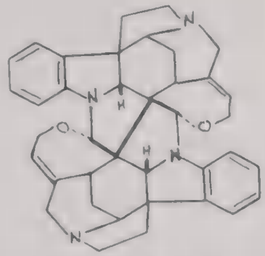

CARACURINE - II

(275)

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CHAPTER 7

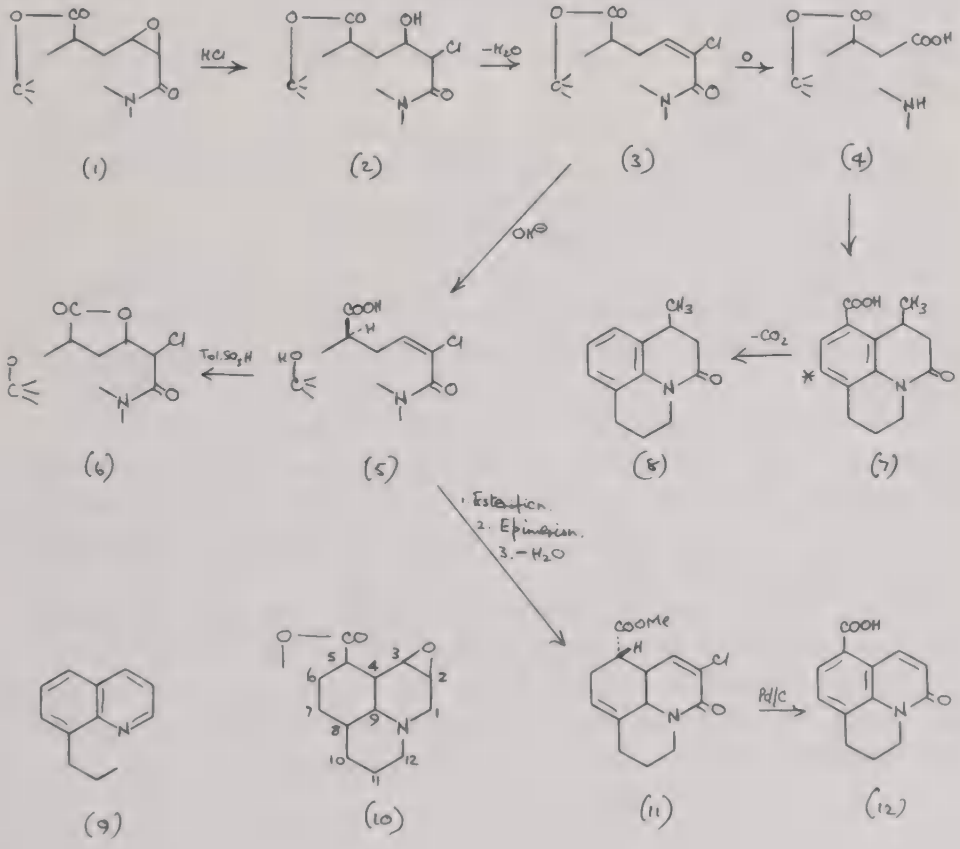
THE LYCOPODIUM ALKALOIDS

The canadian club moss, *Lycopodium annotinum* and related species, which are very primitive plants, contain several closely related alkaloids, which comprise a family structurally unrelated to any other.

Annotinine (29)

This is the principal alkaloid of *L. annotinum*, and has the composition $C_{16}H_{21}O_3N$. It contains a basic tertiary nitrogen atom not present as —NMe—, a γ-lactone system and an epoxide ring that is easily opened by hydrochloric acid to a chlorohydrin. Oxidation of the alkaloid with permanganate gives a lactam $C_{16}H_{19}O_4N$ of part structure (1) which may be converted into the chlorohydrin (2), the anhydro compound (3)[10] and the amino acid (4).[12] The relationship of the lactone ring to the α,β-unsaturated lactam system is demonstrated[12] by hydrolysis of the lactone (3) to the hydroxy acid (5) and the cyclization of this to the saturated lactam (6) containing a new γ-lactone system (the fact that this lactone ring can be formed using the *O*-acetyl ester of the acid (5) confirms the closure of a *new* ring). Palladium dehydrogenation of the amino acid (4) affords the lactam (7), the structure of which is confirmed by total synthesis and by decarboxylation to (8).[13, 15]

Selenium dehydrogenation of annotinine gives a good yield of 8-n-propylquinoline (9), suggesting that the alkaloid contains the perhydrojulolidine system (10), and this is confirmed by the dehydration of the methyl ester of the hydroxy acid (5) to the anhydro ester (11) and the dehydrogenation of this to the acid (12), which can be decarboxylated to the known 1,8-trimethylenequinolone. The composition of annotinine indicates that the carbon skeleton of the alkaloid must be tetracyclic, and accordingly a carbon bridge must be added to the part


HCl
−H₂O
O
(1)
(2)
(3)
(4)
OH⊖
Tol.SO₃H
−CO₂
(6)
(5)
(8)
(7)
1. Esterification.
2. Epimerisation.
3. −H₂O
Pd/C
(9)
(10)
(11)
(12)

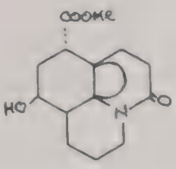
structure (10). One point of attachment of this bridge must be C-4, since this carbon atom must be quaternary, as the methyl ester of the amino acid (4) is very resistant to hydrolysis. The other point of attachment is identified as C-9 by the following process of elimination.

The hydroxy acid (5) can be converted by esterification, epimerization and reduction into the hydroxy ester (13) and this may be oxidized to the ketone (14). This oxidation indicates the second point of attachment of the γ-lactone ring in annotinine, since the other possible point of attachment, C-9, would give a tertiary-alcoholic acid. The selenium dioxide oxidation of the ketone (14) affords the conjugated unsaturated keto ester (15), a pair of epimeric hydroxy derivatives of this (16) and the doubly unsaturated keto ester (17), structures being assigned to the compounds on spectroscopic grounds, and on the basis of the production of one of the epimers of (16) by the alkaline hydrolysis of the dibromide (18), obtained by direct bromination of the ketone (14). The structure assigned to the ester (15) is further supported by the conversion of its sodium borohydride reduction product (19) back to the ketone (14) in alkali.

As a result of these findings it may be concluded that the second point of attachment of the carbon bridge in annotinine cannot be at any of the following positions: 1 (lactam carbonyl), 2, 3, 4, 5, 8, 10 (double bond at a bridge-head forbidden) and 7 (ketone carbonyl). Positions 11 and 12 may also be eliminated, as one of the epimers of (16) gives succinic acid (from carbon atoms 8, 10, 11 and 12) on oxidation under mild conditions. Only C-9 thus remains for the attachment of the bridge.

As annotinine contains a C—CH_3 group the bridge could have the structure —CH_2—CHMe—, —CHMe—CH_2— or —CMe_2— but the arrangement shown in structure (20) is the only one that allows a rational formation of the lactam (7) on dehydrogenation of the amino acid of part structure (4).

This amino acid may be assigned the complete structure (21), which may also be drawn as in (21A), from which it will be seen that no migration of groups is required during the transformation of this into the lactam (7), which may be represented as in (21) → (26). Annotinine may thus be represented by the complete formula (20).



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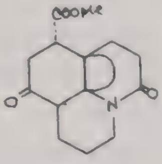

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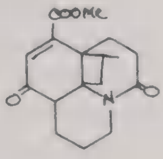

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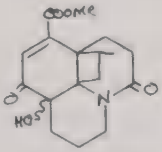

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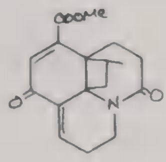

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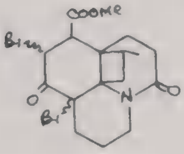

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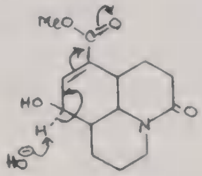

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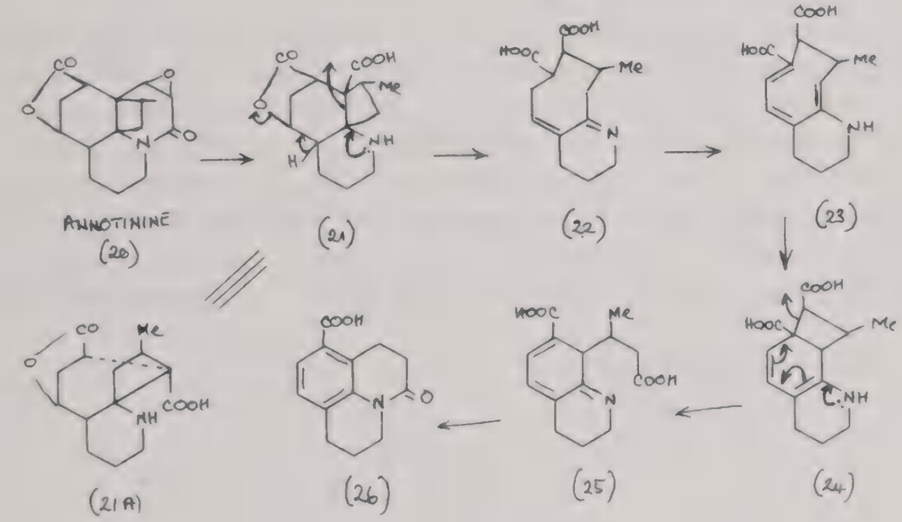


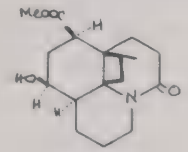
Stereochemistry In view of the ease with which the hydroxy acid of part structure (5) may be epimerized, the carbonyl substituent at C-5 in (20) must occupy the less stable position. The hydrogenation of the unsaturated keto ester (17) would be expected to proceed with addition of hydrogen on the least hindered side of the molecule, which is *trans* to the C-4:C-9 bridge, to give the hydroxy ester (27), and this is identical with the ester derived directly from the hydroxy acid (5), having the unepimerized annotinine structure.

When annotinine is treated with alkali and then with acid, annotinine hydrate (28) is obtained by opening of the lactone ring, epimerization at C-5 and the establishment of a new γ-lactone system as a result of opening of the epoxide ring by the carboxylate ion. The epoxide ring may thus be placed on the same side of the molecule as the 4,9-carbon bridge, and annotinine may be given the complete structure (29).[15] This has been confirmed by x-ray crystallographic studies.[11]

Bases of the Lycopodine Group

Closely related to annotinine, but with a slightly different carbon skeleton, is a group of bases comprising lycopodine (35), acrifoline (36) annofoline (37), fawcettiine (41), clavolonine (42), lycofoline (46) and lycodoline (45).

Lycopodine (35) This base has the composition $C_{16}H_{25}ON$ and contains a saturated carbonyl group, one *C*-methyl group and a tertiary nitrogen atom; it must accordingly be tetracyclic. It reacts with cyanogen bromide to give two isomeric *N*-cyanobromo compounds, which result from fission of each of two similar C—N bonds. One of these products may be hydrolysed to an alcohol $C_{17}H_{26}O_2N$, which is oxidizable to an acid $C_{17}H_{24}O_3N$, and must thus be a primary alcohol. This acid on reduction at the ketonic carbonyl group with sodium borohydride gives a lactone, and the carbonyl group in the parent alkaloid



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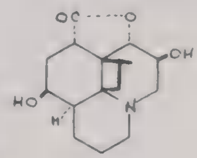

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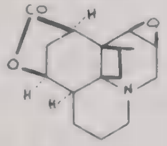


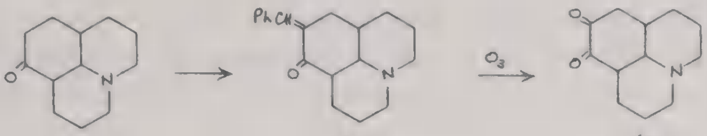
ANNOTININE
(29)

must thus be separated from the nitrogen atom by three or four carbon atoms. Assuming, in view of the origin of lycopodine, that the base contains a perhydrojulolidine system as found in annotinine, the above evidence is compatible with the part structure (30).[9]

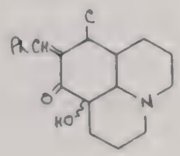
Lycopodine itself contains three enolizable hydrogen atoms as shown by deuterium exchange studies, and it can be converted into a benzylidene derivative (part structure 31) which on ozonolysis gives an enolized α-diketone (32). Selenium dioxide oxidation of the benzylidene derivative, however, gives a hydroxy compound (33) which on ozonolysis yields an unenolized α-diketone (34), and this suggests that the C-5 in (34) is at a bridge-head, in which case enolization would be forbidden. This leads to the formula (35) for lycopodine, the position of the *C*-methyl being assigned by analogy with annotinine (7).[8]

Acrifoline (36) This base, also from *L. annotinum*, has the composition $C_{16}H_{23}O_2N$ and contains one ketonic carbonyl group, one secondary alcoholic group, one double bond and one *C*-methyl group. Hofmann degradation of acrifoline methiodide gives a conjugated diene, which on ozonolysis furnishes formaldehyde. Selenium dioxide oxidation of acrifoline yields an unsaturated ketone that spectroscopic evidence shows to contain the system CH=CMe—C=O, and Oppenauer oxidation of dihydroacrifolinol (the product of catalytic and borohydride reduction of the alkaloid) affords a diketone, in which both carbonyl groups are shown by spectral evidence to be present in at least six-membered rings. On this evidence acrifoline is assigned the structure (36); the double bond is not placed at position C-8 : C-10 since the alkaloid is not an allylic alcohol.[7]

Annofoline (37) This base, $C_{16}H_{25}O_2N$, on selenium dioxide oxidation gives an α,β-unsaturated ketone shown by spectral studies to contain the system C—CH=CMe—CO—. Wolff–Kishner reduction affords dihydrodeoxyannofoline, in which the secondary alcoholic system can be oxidized by chromic acid, the product, deoxyannofoline $C_{16}H_{25}ON$, being further oxidizable by selenium dioxide to an enolized α-diketone. The structure (37) is thus suggested and supported by the reactions shown in formulae (37)–(40).[2, 6]



(30) (31) (32)



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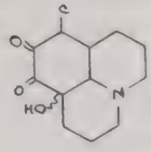

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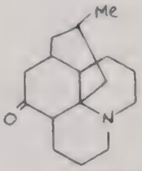
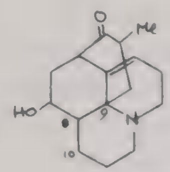
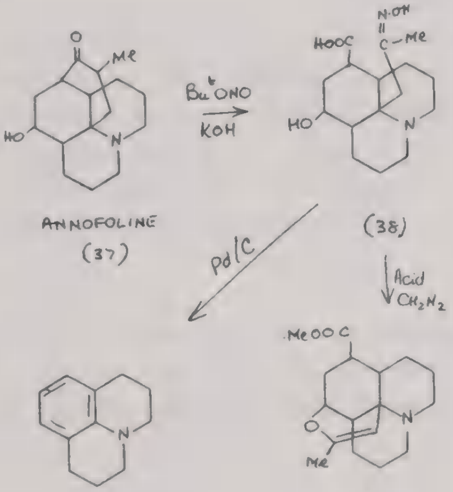


LYCOPODINE
(35)



ACRIFOLINE
(36)



ANNOFOLINE
(37)

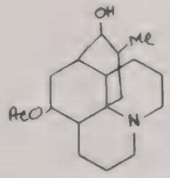
(38)

(40) (39)

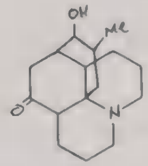
Clavolonine (42) and fawcettiine (41) These two alkaloids, from *L. Clavatum* and *L. Fawcettii* respectively, have the compositions $C_{16}H_{25}O_2N$ (isomeric with annofoline) and $C_{18}H_{29}O_3N$. Fawcettiine contains one hydroxyl and one acetoxyl group, the latter accounting for the increased carbon content. Oxidation of the base to a ketone dehydrofawcettiine followed by hydrolysis of the —OAc group yields annofoline (37). Hydrolysis of fawcettiine yields deacetylfawcettiine, which may be reacetylated to isofawcettiine in which the positions of OH and OAc are reversed; this new base on oxidation to a ketone gives *O*-acetylclavolonine. Accordingly, fawcettiine and clavolonine may be given the structures (41) and (42) respectively, and in support of these structures may be cited the reduction of clavolonine to a pair of epimeric diols, one of which is deacetylfawcettiine. Although annofoline is identical with deacetyldehydrofawcettiine, acetylannofoline is not identical with dehydrofawcettiine; since annofoline exists in both keto- and hemiketal forms, acetylation must be assumed to give the hemiketal acetate (43).

Lycodoline (45) This base is isomeric with and contains the same functional groups as annofoline. It reacts with ethyl bromoacetate to give a quaternary salt that affords a δ-lactone on acid hydrolysis, indicating that the hydroxyl group is probably at C-2, 4, 8 or 11. Wolff–Kishner reduction yields deoxylycodoline, which on dehydration gives anhydrodeoxylycodoline (34), obtainable by successive Oppenauer oxidation and Wolff–Kishner reduction of acrifoline (36); the hydroxyl group must thus be at C-4. The ketonic carbonyl group is assumed to be at C-7, which bears an oxygen substituent in all the other bases of this group, and lycodoline is accordingly represented by the structure (45).[5]

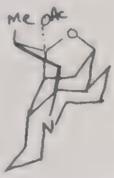
Lycofoline (46) Sodium borohydride reduction of acrifoline (36) in alkaline solution affords a mixture of two epimeric alcohols (46) one of which is identical with the alkaloid lycofoline.[1]



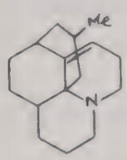
FAWCETTINE
(41)



CLAVOLONINE
(42)



ANNOFOLINE ACETATE
(43)



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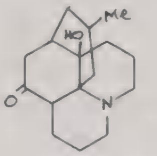
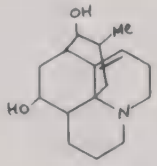


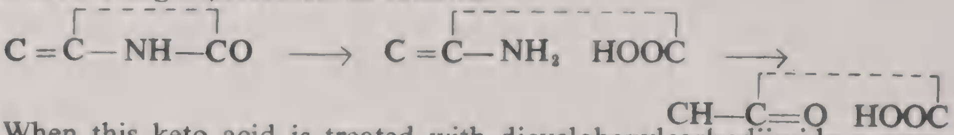
LYCODOLINE
(45)



LYCOFOLINE
(46)

The Obscurines (52) and (54)

The base α-obscurine, from *L. obscurum*, has the composition $C_{17}H_{25}ON_2$ and contains one NMe group (basic), one —NH—CO— group and one double bond. On treatment with nitrous acid the NMe group is replaced by N.NO and the product may be hydrolysed to a secondary amine. Vigorous acid hydrolysis of this secondary base proceeds with loss of the non-basic nitrogen atom and affords a keto acid as a result of the fission of a lactam system. This lactam ring must therefore contain the nitrogen atom attached to a double bond, the fission being represented as follows.



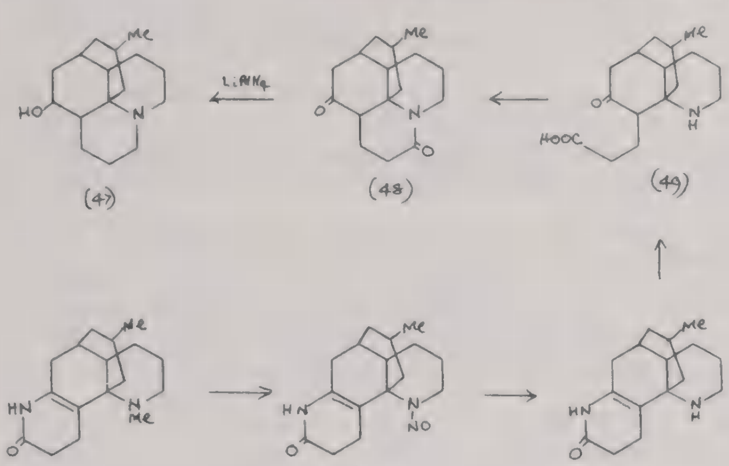
$$C{=}C{-}NH{-}CO \longrightarrow C{=}C{-}NH_2 \quad HOOC \longrightarrow CH{-}C{=}O \quad HOOC$$

When this keto acid is treated with dicyclohexylcarbodiimide a new lactam ring is closed between the carboxyl group and the secondary amino group derived, originally, from the tertiary basic centre. The lactam so formed on reduction with lithium aluminium hydride yields dihydrolycopodine (47). Reasoning backwards from this result through the structures (49)–(52) α-obscurine must be assigned the structure (52). The reader should satisfy himself that corresponding structures derived from the lactam (53) are not permissible, involving as they do a double bond at a bridge-head.

β-Obscurine is the corresponding dehydro compound (54).[4]

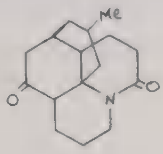
Lycodine (58) This base also belongs to the obscurine group and is obtainable from lycopodine (55) via β-bromocyanolycopodine (56) as shown in the formulae (55)–(58).[3]

Selagine (59) This alkaloid contains a primary amino group and an α-pyridone ring, shown by NMR studies to be 5,6-disubstituted. It also contains two reducible trisubstituted double bonds. Treatment with nitrous acid affords the alcohol selaginol and periodate–permanganate oxidation of tetrahydroselaginol gives 3-carboxy-2-ethyl-5-methylcyclohexanone (61) and accordingly, selagine is formulated as (59) and tetrahydroselaginol as (60).[14, 16]



(47) (48) (49)

α-OBSCURINE (52) (51) (50)



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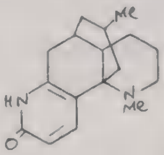
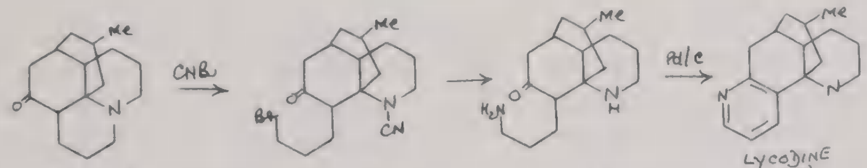
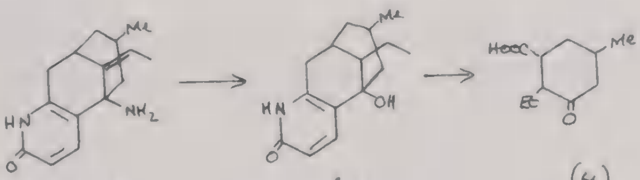


β-OBSCURINE (54)



LYCOPODINE (55) (56) (57) LYCODINE (58)



SELAGINE (59) (60) (61)

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CHAPTER 8

ALKALOIDS OF THE DITERPENE SERIES

Two general groups of diterpene alkaloids may be distinguished namely the bases of the garryine–atisine group, the structures of which were elucidated by classical chemical methods, and more complex bases of the lycoctonine–delcosine series, whose structures were only completely unravelled after x-ray crystallographic studies.

THE GARRYINE-ATISINE BASES

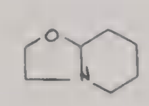
Several *Garrya* species have been found to contain alkaloids, the bases so found being garryine, garryfoline, veatchine and cuauchichicine, all of which are isomeric, having the composition $C_{22}H_{33}O_2N$. The first three bases contain the same functional groups, namely a tertiary nitrogen atom not bearing a methyl group, one $C{=}CH_2$ group, one $C—CH_3$ group and one hydroxyl group, whereas cuauchichicine contains two $C—CH_3$ groups and a carbonyl group. The second oxygen atom in all four alkaloids, together with the nitrogen, forms part of a carbinolamine ether system. The composition of the bases and the determination of the functional groups show that these alkaloids must be hexacyclic.

Reduction of the bases with lithium aluminium hydride proceeds with ring opening and the production of bases containing the group

N—CH_2CH_2OH and this is conveniently explained by assuming that the bases contain the system (1).[13] Selenium dehydrogenation of veatchine and garryine affords 7-ethyl-1-methylphenanthrene (2) and an azaphenanthrene, shown by x-ray studies to have the structure (3), which was confirmed by synthesis, suggesting that the part structure (4) is probably present in the alkaloids, and garryine could be further represented by (5) or (6). One carbon atom must be added to (5) or (6) to furnish a complete skeleton for garryine, and in view of the production of the two ethyl compounds (3) and (2) during dehydrogenation it is probable that this atom in the alkaloids links the carbon marked with an asterisk in (5) and (6) with one of the angular positions of the phenanthrene skeleton, thus completing the necessary sixth ring. Of the two available positions one affords a skeletal structure based on that of the naturally occurring diterpene phyllocladene (7) and is thus preferred, and the structures (8) and (9) become likely for garryine and veatchine. The hydroxyl group is placed on the two-carbon bridge, since oxidation of veatchine leads successively to two isomeric oxoveatchines, and two oxoveatchine carboxylic acids, with fission of the bridge, and these acids contain the phenanthrene skeleton intact since they yield pimanthrene (11, $R=CH_3$) and the acid (11, $R=COOH$) on dehydrogenation.[13] The two oxoveatchine carboxylic acids have the structure (10) and the isomeric structure bearing the lactam carbonyl group at the position shown by an asterisk. The acids both form anhydrides showing infrared absorption of substituted glutaric anhydrides, thus confirming the five-membered nature, and hence location, of the sixth ring in the alkaloids.

Veatchine may be isomerized in boiling methanol, the base acting itself as a catalyst, to give garryine, which is assigned the less crowded carbinolamine ether structure (9), veatchine being represented by (8); these assignments are supported by pK_a measurements, which indicate that veatchine is a stronger base than garryine, presumably since steric hindrance in (8) favours formation of a quaternary hydroxide (12) rather than a hydroxy base such as (13) on hydration.

Garryfoline is the epimeric alcohol corresponding to veatchine and can be isomerized in boiling methanol to isogarryfoline, the epimer of garryine. Cuauchichicine contains a carbonyl group and no reducible double bond, and, since its infrared absorption is characteristic of a five-membered cyclic ketone and it can be isomerized by boiling with



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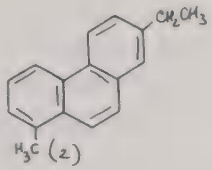

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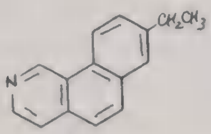

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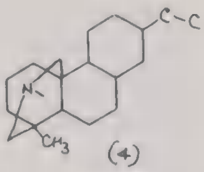

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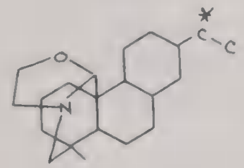

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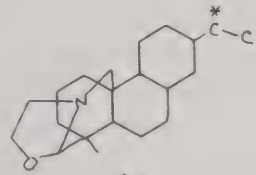

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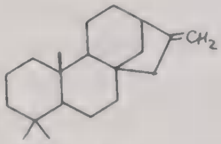

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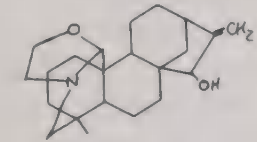
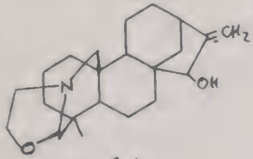
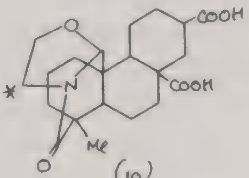


(8)
VEATCHINE



(9)
GARRYINE



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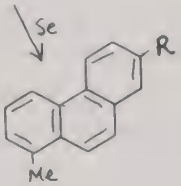

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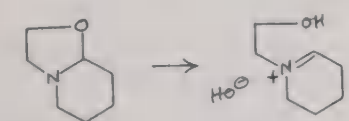

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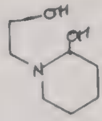
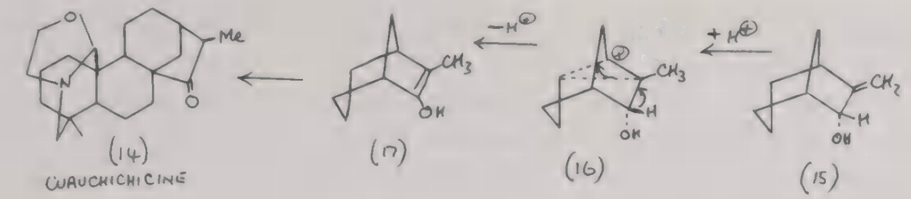


(13)

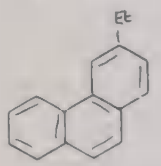
methanol to isocuauchichicine, it may be formulated as in (14). This alkaloid may be prepared by the acid-catalysed isomerization of garryfoline, presumably via the non-classical carbonium ion (16), in which all the participating centres lie in the same plane; by contrast the epimer of garryfoline, namely veatchine, is stable to mineral acids.

Atisine The structure of this base from *Aconitum heterophyllum* Wall, for which an incorrect structure had earlier been suggested, followed from the above work on the *Garrya* bases. It is isomeric with garryine and veatchine and contains the same functional groups. Like veatchine it is easily isomerized, the product being isoatisine. On dehydrogenation with selenium it affords products isomeric with (2) and (3), namely 6-ethyl-1-methylphenanthrene (18) and the base (19), suggesting that atisine may have the structure (20), differing from veatchine only in the arrangement of the two-carbon bridge bearing the methylene and hydroxyl groups. This is supported by oxidation of atisine to two oxo compounds, which are γ- and δ-lactams analogous to the two oxoveatchines, and the further oxidation of these to dicarboxylic acids (21) which behave as cyclohexane-1,4-dicarboxylic acids.[5, 8] A by-product of the oxidation is the base (22), which may be reduced, acetylated and hydrated to the vicinal diol (23), and oxidation of this affords the keto acid (24). Treatment of this keto acid with trifluoroacetyl peroxide followed by hydrolysis and oxidation yields the keto acid (25) which may be converted into the phenol (26) by bromination and dehydrobromination.[3] This phenol may be further converted into the lactam (27), the mirror image of which is obtainable by the ultraviolet irradiation of podocarpoyl azide (28).[1]

Isoatisine (29) may be isomerized to a mixture of two epimeric ketones of structure (30), differing only in stereochemistry at the asymmetric centre marked with an asterisk, the process resembling the conversion of garryfoline into cuauchichicine. Reduction of the keto group of these, with simultaneous opening of the oxazolidine ring, affords a mixture of epimeric bases (31) which on dehydrogenation yield the base (32) and the phenanthrene (33).[7]



(14) CUAUCHICHICINE (17) (16) (15)



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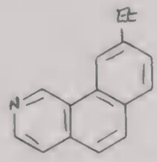

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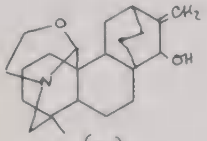
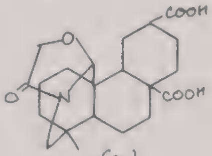


(20) ATISINE



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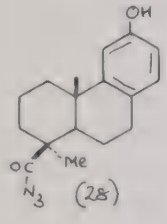

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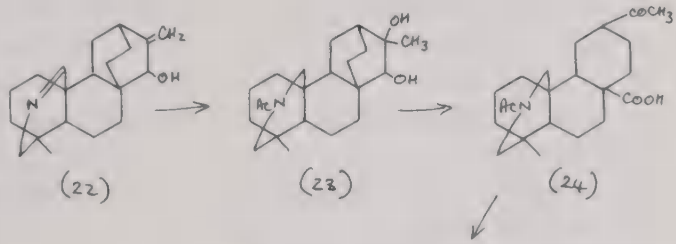
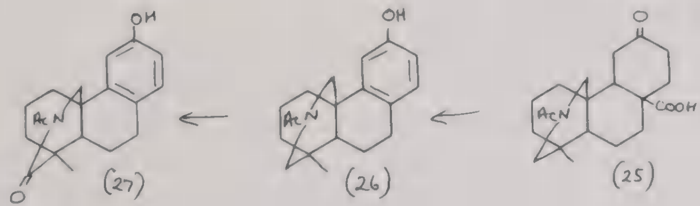
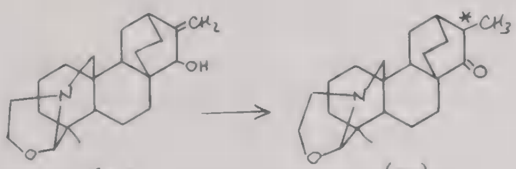


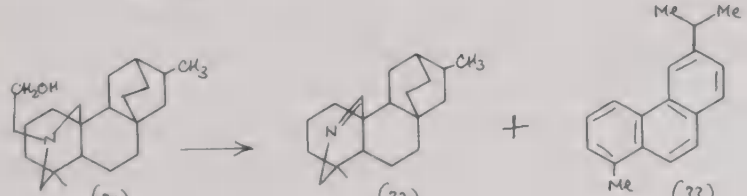
(22) (23) (24)



(27) (26) (25)



(29) ISOATISINE (30)

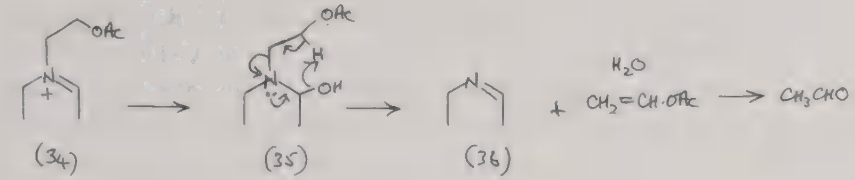


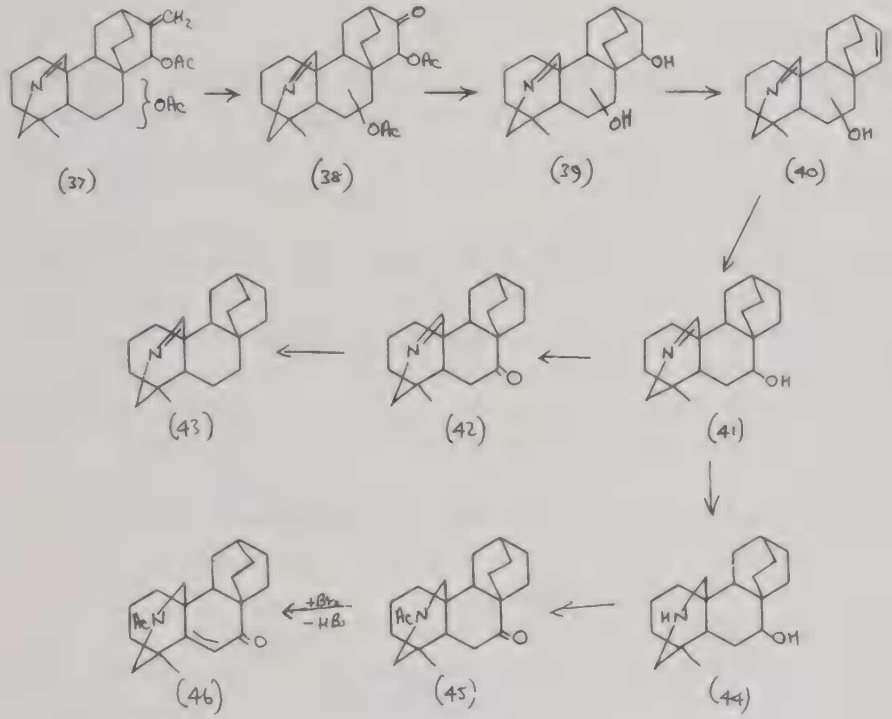
(31) (32) (33)

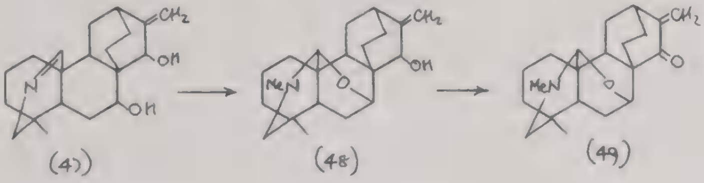
Ajaconine This alkaloid is obtainable from *Delphinium ajacas*, and has the composition $C_{22}H_{33}O_3N$. It contains, like atisine, the groups $C{=}CH_2$ and CH—OH, but also bears a second hydroxyl group. Like atisine also it is reducible with sodium borohydride without loss of oxygen to a dihydrobase and forms imonium salts, indicating the presence in the molecule of a carbinolamine cyclic ether system. The salts may be converted into an *O,O,O*-triacetyl compound with fission of the carbinolamine ether system and this base when gently heated splits off acetaldehyde as in (34) → (36) to give the base (37). This base has been converted by the sequence of reactions shown opposite into the degradation product (43), obtainable also in a similar manner from atisine. In view of the fact that dihydroajaconine can be converted by acid-catalysed isomerization into an α-methylketone, by a process identical with the transformation of isoatisine (29) into the ketone (30), the $C{=}CH_2$ group and one CH.OH group doubtless have the same relationship in atisine and ajaconine and the latter was first formulated as a hydroxyatisine. This view had to be abandoned in the light of further work, however, which revealed that the carbinolamine cyclic ether group involves an oxygen atom attached to C-9; this conclusion was reached in the following way.[4]

The azomethine alcohol (41) may be reduced with sodium borohydride to the secondary amine (44) and this can be subsequently transformed into the *N*-acetylated ketone (45) and finally into the α,β-unsaturated ketone (46). The infrared absorption spectrum of this ketone indicates that the double bond is β,β-disubstituted and the structure (46) is the only possible one satisfying this requirement, as will be seen on inspection of the bridged-carbon skeleton.

That this C-9 hydroxyl group is not free in ajaconine but is bound up in a carbinolamine ether system is indicated by the fact that the methiodide of the base (47), obtained by hydrolysis of the triacetyl compound (37), on treatment with alkali affords a carbinolamine ether (48) which must involve the C-9 hydroxyl, since the product may be oxidized to the non-hydroxylic α,β-unsaturated ketone (49). Since this base (48) and ajaconine have identical pK_a values (10·6) and closely similar optical rotations it may be concluded that their structures are similar. That C-17 and not C-16 is involved in this carbinolamine ether system follows from the conversion of the carbinol (41) into the ether


OAc
+
(34)
OAc
H
OH
(35)
(36)
+
H_2O
$CH_2=CH\cdot OAc \longrightarrow CH_3CHO$


CH_2
OAc
OAc
N
(37)
O
OAc
OAc
N
(38)
OH
OH
N
(39)
OH
N
(40)
N
(43)
N
O
(42)
N
OH
(41)
AcN
O
(46)
+Br₂
− HBr
AcN
O
(45)
HN
OH
(44)


CH_2
OH
OH
N
(47)
CH_2
OH
MeN
O
(48)
CH_2
O
MeN
O
(49)

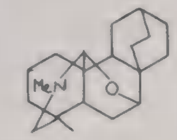
(50) and the oxidation of this to the lactam (51). As experience with other alkaloids of this group has shown that the oxidation of C-17, even when this is already at the oxidation level of an aldehyde, is extremely difficult, the lactam carbonyl must be at C-16 in (51) and accordingly the parent base must be correctly represented by (50).

As the C-9 hydroxyl of the base (47) is bound up in an ether system in ajaconine the second hydroxyl group of this alkaloid must be present in an $N.CH_2CH_2OH$ system and the complete structure (52) may be assigned to the base.[4]

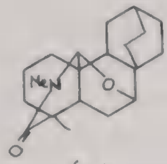
Stereochemistry

Atisine and veatchine belong to the same stereochemical series, as was shown by the conversions of both alkaloids as shown in formula (53) → (58) and in (59) → (58). Ajaconine and atisine have also been related directly to the base (43). In order to secure closure of the carbinolamine ether system of ajaconine the ether oxygen and C-17 must be *cis* diaxial in ring B and this can only be achieved with a *trans* fusion of rings A and B as shown in (60), leaving four possible structures (61)–(64) or their mirror images for the atisine skeleton; of these (61) and (63) have a *trans-anti*-phenanthrene skeleton and (63) can be eliminated since the ketone (65) is readily reducible to a pair of epimeric alcohols, and only one epimer would be expected if the highly crowded arrangement of (63) at C-8 existed in the ketone. Similarly in the *trans-syn* arrangements steric hindrance at C-8 in the ketone (65) is high with the arrangement (62) and low in (64), so that only the skeletons (61) and (64) need be considered further.

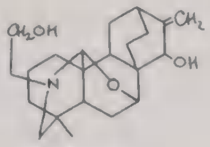
When the carbinolamine ether system between C-17 and C-9 is opened or closed in derivatives of ajaconine, a very large shift in rotation occurs (positive on opening, negative on closing) and spectral data show that the C-9 hydroxyl group of ajaconine resulting from opening of the ring is equatorial. The arrangement (61) offers a reasonable explanation of these findings since in the ring-opened form ring B could adopt the chair conformation with the C-9 hydroxyl equatorial,



(50)

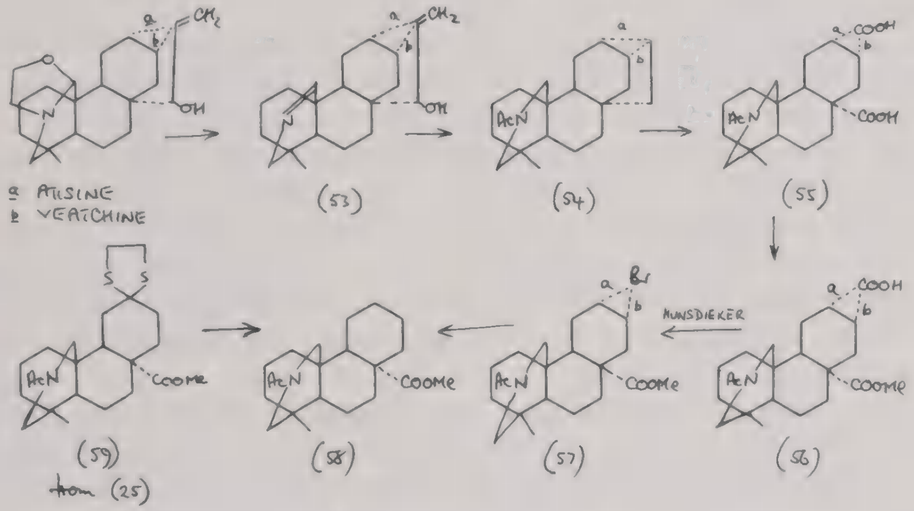


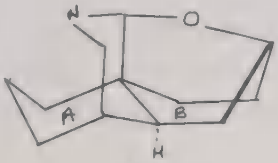
(51)



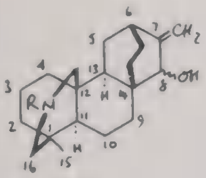
AJACONINE

(52)

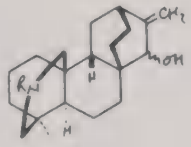




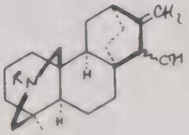
(60)



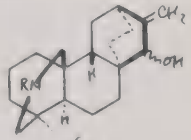
(61)



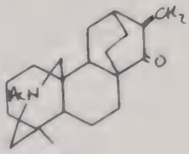
(62)



(63)



(64)

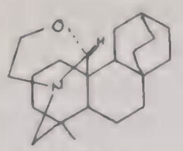


(65)

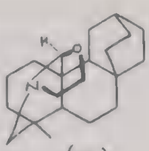
but in the ring-closed form ring B would have to become a boat with the ether oxygen atom pseudo-axial at C-9, as in (60). The arrangement (64) would, however, involve ring B remaining as a boat even in the hydroxylic form and the C-9—oxygen bond would in both types of structure remain pseudo-axial.

Rings E and F can be added to the system of (61) in six different ways according to whether ring E is a boat or chair form with ring F fused in either of two *cis* or one *trans* manner. As great steric hindrance exists between C-17 and C-19 the fact that the oxazolidine ring may be easily reformed from alkaloidal derivatives in which C-17 is trigonal indicates that the oxygen atom of that ring must be on the less hindered side of C-17 (66) rather than on the more hindered side (67). Three arrangements out of the six may be eliminated in this way. In the structure (68) there is a strong steric hindrance between rings A and F and this leaves only (69) and (70) to be considered and there is little difference in hindrance in these two forms; such difference as there is should favour (70) over (69).

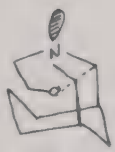
The conversion of garryfoline and veatchine into the ketones (71) and (72) establishes the absolute configuration of the bases at C-8 and C-13, since the optical rotatory dispersion curves of these are very similar to that of the ketone (73), of established configuration, derived from the phyllocladene series. Further, garryfoline (74) has been degraded as shown to the hydrocarbon stevan-B (80) obtained also from the degradation of the diterpenes steviol (81) and kaurene (82), thus



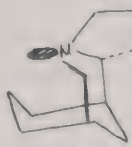
(66)



(67)



(68)



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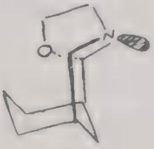

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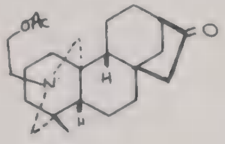
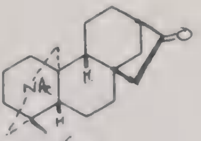
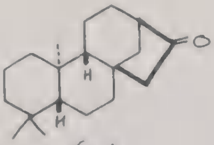


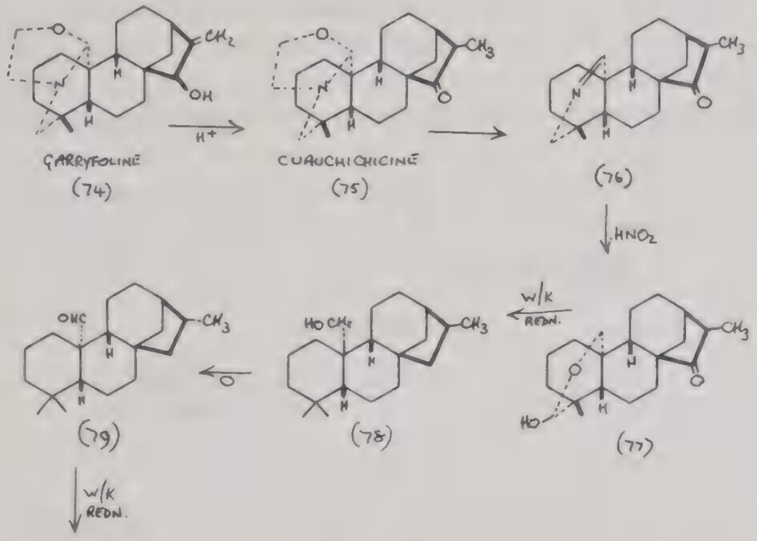
(71)



(72)



(73)



GARRYFOLINE (74)

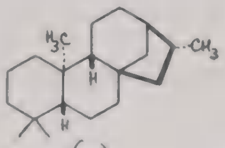
CUAUCHICHICINE (75)

(76)

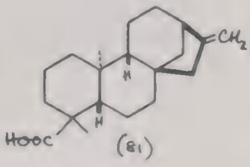
(77)

(78)

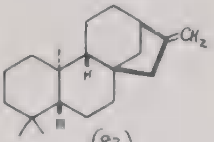
(79)



(80)



(81)



(82)

establishing the absolute stereochemistry of garryine (83), veatchine (84), atisine (85) and ajaconine (86).[12]

Another alkaloid derived from the atisine skeleton, but with additional bridging is hetisine, the structure (87) for which was only determined crystallographically.[9] Unlike the other bases of this group hetisine may be successfully subjected to Hofmann degradation, the product being a normal methine base containing two double bonds. Vigorous quaternization, however, affords a methiodide isomeric with the normal salt, and this on degradation yields a methine base containing only one double bond. These new derivatives contain a *C*-methyl group, and are believed to be derived from the hemiketal (89), which could arise from hetisine as shown, via the hydroxy ketone (88).[6, 14]

COMPLEX ALKALOIDS

The second group of alkaloids defied structural elucidation by the classical chemical methods and it was only when the structure of lycoctonine was determined by x-ray crystallographic methods,[10] that the relationships within the group could be interpreted on a rational basis. Lycoctonine has the structure (94) and may be formally regarded as being derived from atisine (90) by loss of the methylene group (possibly by oxidation), Wagner–Meerwein rearrangement and cyclization between C-9 and C-17 followed by other oxidative and reductive changes and *O*-methylations, as shown essentially in formulae (90)–(94), though the processes represented there are only an indication of the sort of changes that could occur.[2, 11]

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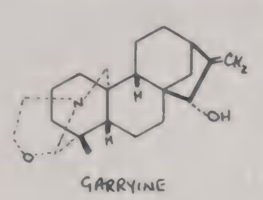
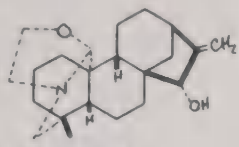
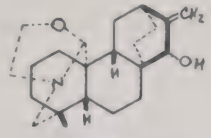

GARRYINE
(83)


VEATCHINE
(84)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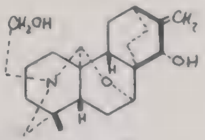
(85)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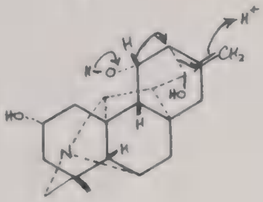
(86)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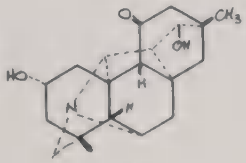
(87)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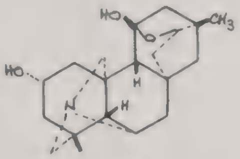
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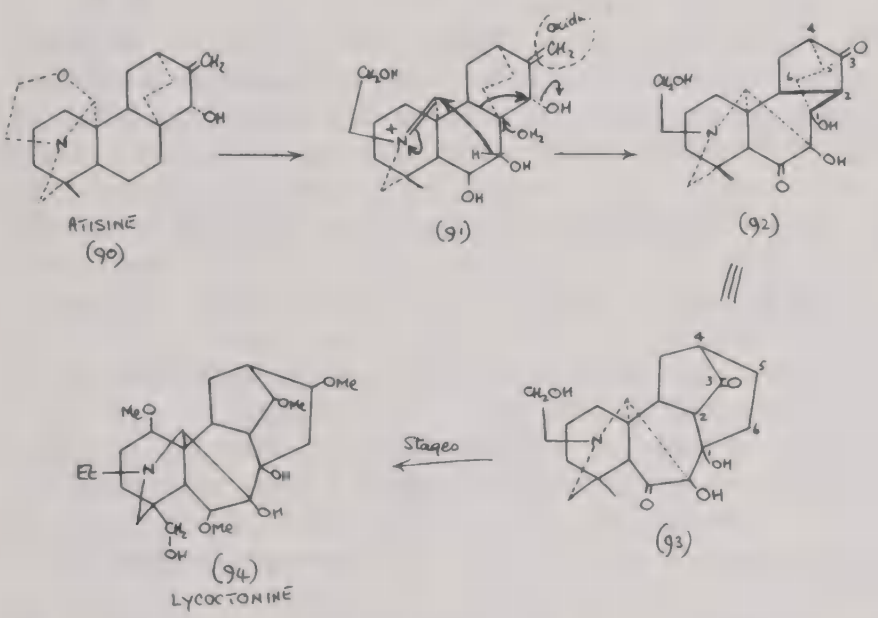

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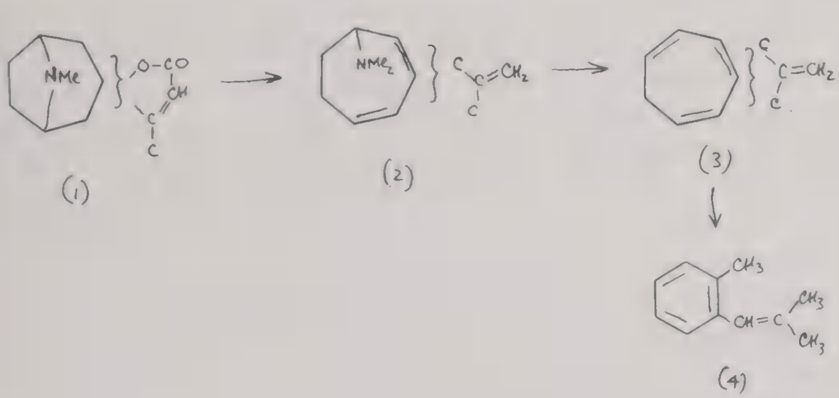
CHAPTER 9

MISCELLANEOUS ALKALOIDS

1. Dioscorine

This alkaloid may be isolated from the tubers of *Dioscorea hispida* Dennst. and *D. Hirsuta* Blume. It has the composition $C_{13}H_{19}O_2N$ and contains one *N*-methyl group. The base is not extractable from alkaline solution after warming, but is recovered unchanged on acidification, suggesting the presence in the molecule of a lactone ring, which was thought to be unsaturated since, like cardiac aglycones, the base gives a positive Legal colour test with sodium nitroprusside; that this double bond is α,β to the lactone carbonyl group was suggested by the ready reduction of dioscorine with sodium amalgam.[7] These deductions were confirmed by infrared absorption studies[9] which also indicated that the lactone ring is at least six membered and contains no *alpha* substituent, since decarboxylation of the corresponding hydroxy acid affords a base containing the system $C—C(=CH_2)—C$.

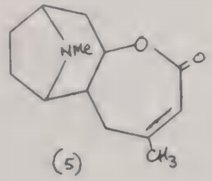
Hofmann degradation of dioscorine proceeds with hydrolysis, dehydration and decarboxylation to afford a triply unsaturated base $C_{13}H_{21}N$ and further degradation affords a $C_{11}H_{14}$ hydrocarbon that rapidly polymerizes and is converted by hydrogen bromide into an isomeric *o*-alkenyltoluene, oxidizable to *o*-toluic acid. The alkaloid was assumed to be a derivative of tropane (1), on the basis of which, the degradations were explained by the part structures (1) → (4), with which the infrared spectral data were not incompatible. Hydrogenation of the nitgrogen-free product $C_{11}H_{14}$ (3?) yields a saturated product $C_{11}H_{22}$ not identical with i-butylcycloheptane. On the basis of the close


NMe
O-CO
CH
C
C
(1)
NMe₂
C
C=CH₂
C
(2)
C
C=CH₂
C
(3)
CH₃
CH=C
CH₃
CH₃
(4)

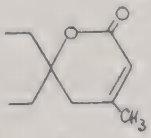
similarity but not identity of the spectra of the base $C_{13}H_{27}N$ (obtained from the Hofmann degradation product) and 3- and 4-dimethylamino-i-butylcycloheptane, however, the structure (5) was tentatively advanced for the alkaloid.

The reduction of dioscorine with lithium aluminium hydride affords an unsaturated diol (dioscorinol), one hydroxyl group of which must be allylic since it may be removed by hydrogenolysis with sodium and ammonia and the product, deoxydioscorinol, may be reduced to dihydrodeoxydioscorinol, which is a tertiary alcohol. These results are only explicable on the assumption that dioscorine contains the system (6). On the basis of a tropane structure for the alkaloid, in view of the fact that it shows none of the properties of a carbinolamine ester, only the three structures (7), (8) and (9) need be considered, and of these (7) can be eliminated as it contains a plane of symmetry whereas dioscorine is optically active.[8, 10]

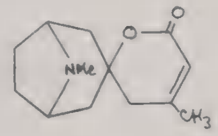
Dioscorinol on ozonolysis affords glycollic aldehyde (confirming the presence of the system $HOCH_2CH{=}C$) and a methyl ketone, which undergoes dealdolization in alkalis to yield acetone and a ketone $C_8H_{13}ON$ originally claimed[1, 4] to be identical with (+)-tropan-2-one prepared from cocaine.[2] These results apparently unambiguously identified dioscorine as the base (8). The identity of the two ketones has, however, since been disproved. The methiodide of the ketone $C_8H_{13}ON$ obtained from dioscorinol is extremely sensitive to sodium bicarbonate, undergoing Hofmann degradation to a base $C_9H_{15}ON$ and a neutral product C_7H_8O, and the methiodide of the first of these readily gives the second under similar mild conditions. Spectral evidence revealed that the neutral compound contains a cross-conjugated chromophore $H_2C{=}C{-}CO{-}CH{=}CH{-}$ and, as it is smoothly isomerized by palladized charcoal to *o*-cresol (10), it may be assigned the structure (11). The initial Hofmann degradation product $C_9H_{15}ON$ is an α,β-unsaturated ketone and must be the base (12) or the isomeric (13), spectral evidence favouring the former. Racemic material of structure (12) was synthesized from *o*-methoxybenzaldehyde (14) via the intermediates (15) and (16). Hydrogenation of the base (12) affords 2-dimethylaminocyclohexanone (17), identical with material prepared by the Mannich reaction from cyclohexanone.[5]



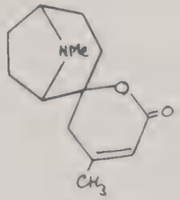
(5)



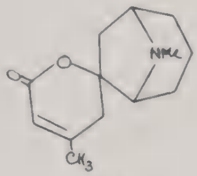
(6)



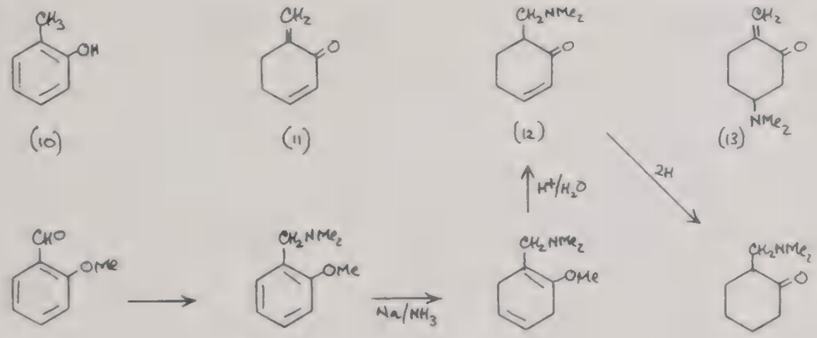
(7)



(8)



(9)



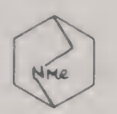
(10) (11) (12) (13)

(14) (15) (16) (17)

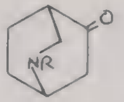
The ketone $C_8H_{13}ON$ from dioscorinol must therefore have the quinuclidine structure (18, R = Me); it is reducible by the Wolff–Kishner process to the base (19), synthesized from *p*-aminobenzoic acid via the intermediates (20) and (18, R = H). Dioscorine itself may thus be assigned the structure (21).[5]

2. Cryptopleurine

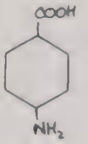
This alkaloid is obtainable from *Cryptocarya pleurosperma*, contains a tertiary nitrogen atom and three methoxyl groups and was identified by x-ray crystallographic analysis as the base (28).[6] This structure has been confirmed by a total synthesis of the racemic base by the route shown in (22) → (28).[3]



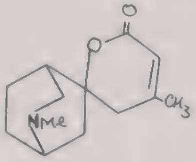
(19)



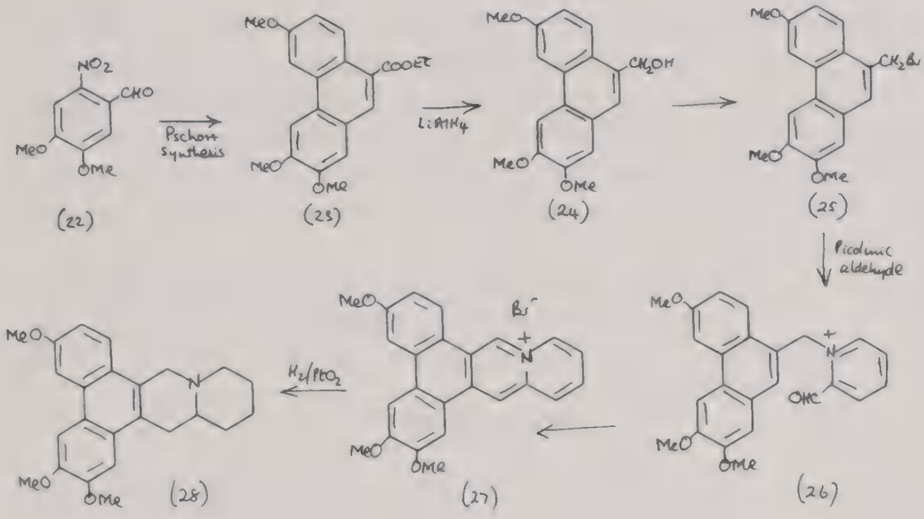
(18)



(20)



DIOSCORINE
(21)



3. Himbacine

A number of closely related bases is obtained from *Galbulimima baccata* and related species. Of these himbacine $C_{22}H_{35}O_2N$ contains one *N*-methyl group, two *C*-methyl groups, one γ-lactone ring and one reducible 1,2-disubstituted double bond. On selenium dehydrogenation it yields 2-ethyl-3-methylnaphthalene (29), and 2-ethyl-6-methyl pyridine (30). It is reduced by lithium aluminium hydride to a diol (31) which may be dehydrated and catalytically reduced to the ether (32) and this in turn, on Hofmann degradation, yields a mixture of two isomeric methine bases (33) and (34) differing only in the position of the double bond introduced during fission of the nitrogen-containing ring. Oxidation of these bases affords a C_{16} acid (35) and a C_{15} acid (36) and the former is converted through the latter into the acid (37) by a two-step Barbier–Wieland degradation. The structure of the acid (37) is revealed by selenium dehydrogenation to 3-ethyl-2-methyl naphthalene (29). The structures of the acids (35) and (36) and the isomeric methine bases (33) and (34) follow logically from that of the acid (37) and in turn lead to the unambiguous expansion of (31) to (39) for the cyclic ether and to the structure (40) for dihydrohimbacine.[11]

Himbacine itself contains a double bond and must have the structure (41) since it can be oxidized directly to a lactonic acid $C_{14}H_{20}O_4$ (38) obtainable also by the oxidation of the acid (37).[11]

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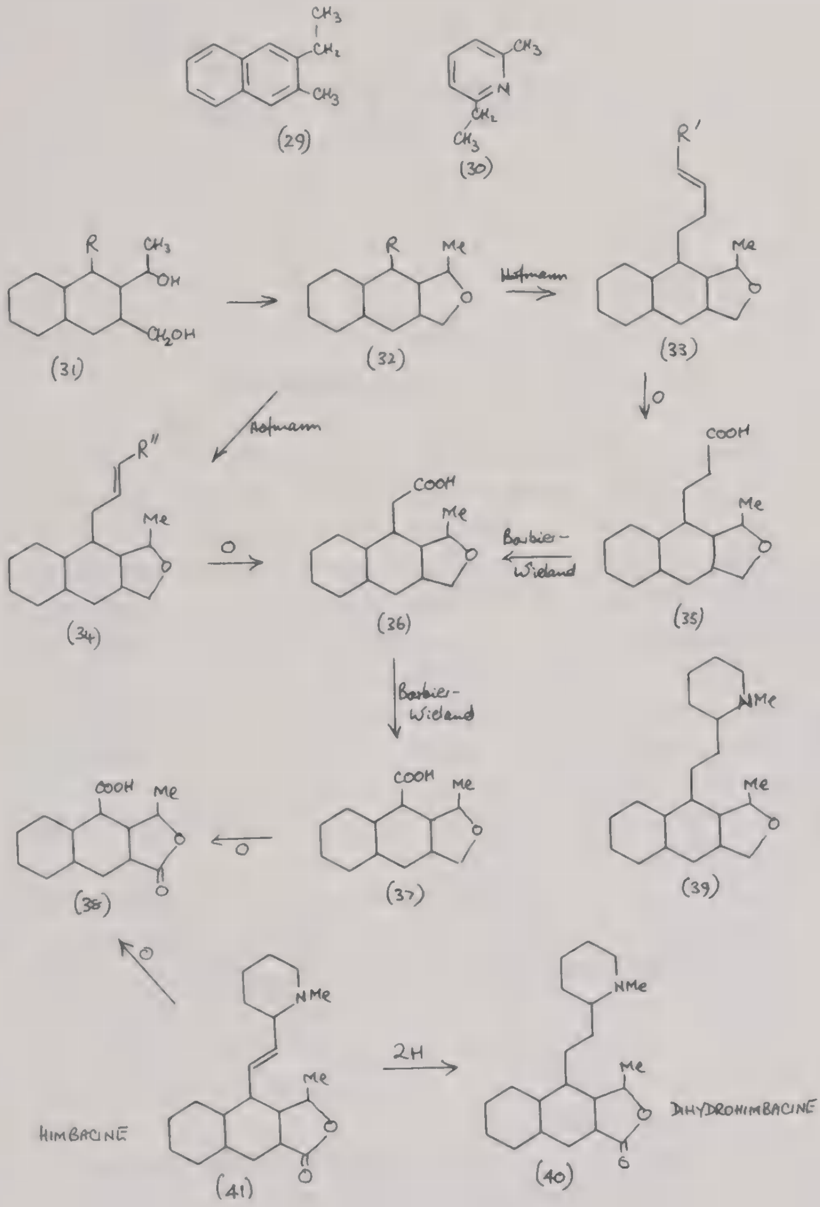

CH3
CH2
CH3
(29)
CH3
N
CH2
CH3
(30)
R
CH3
OH
CH2OH
(31)
R
Me
O
(32)
Hofmann
R'
Me
O
(33)
O
COOH
Me
O
(35)
Hofmann
R''
Me
O
(34)
O
COOH
Me
O
(36)
Barbier-Wieland
Barbier-Wieland
COOH
Me
O
(37)
O
COOH
Me
O
O
(38)
NMe
Me
O
(39)
O
NMe
Me
O
O
HIMBACINE
(41)
2H
NMe
Me
O
O
DIHYDROHIMBACINE
(40)

CHAPTER 10

THE BIOGENESIS OF ALKALOIDS

THE INDOLE ALKALOIDS

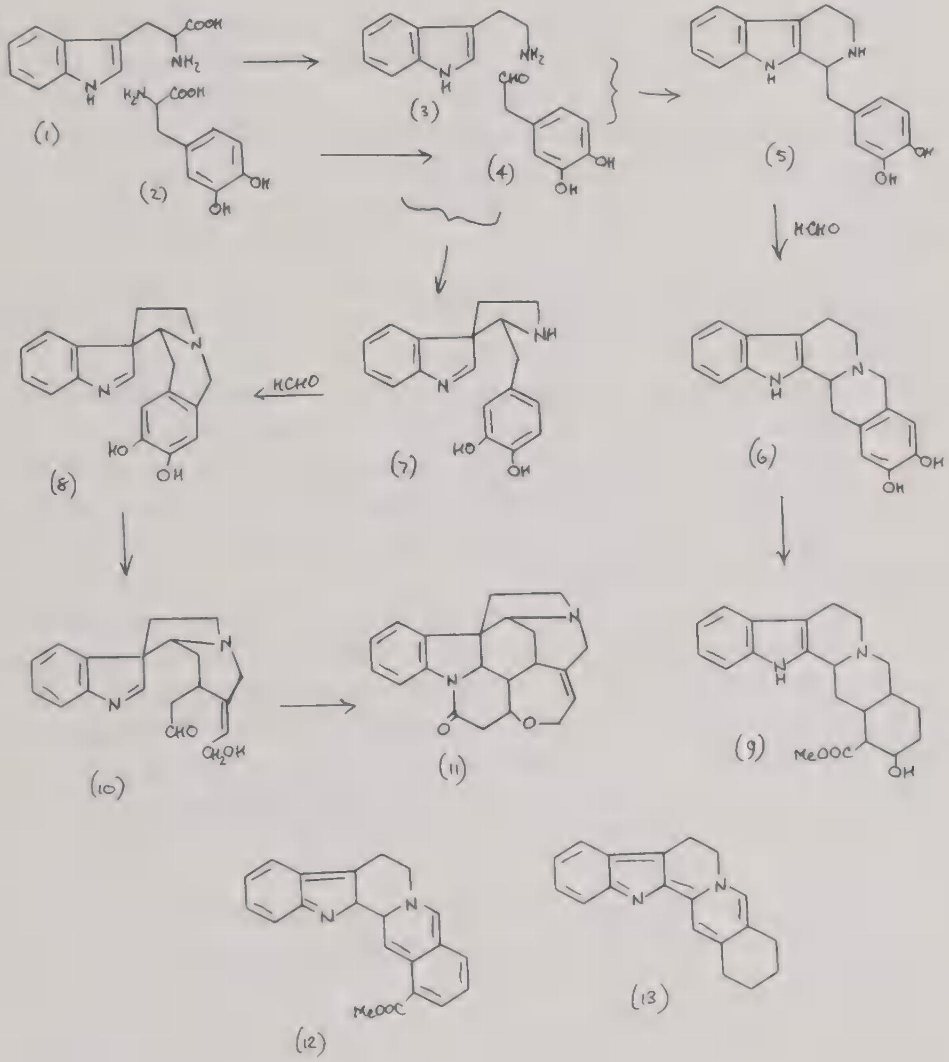
Some theories of the biogenesis of the indole alkaloids were set out in Part I[7] of this work; briefly these postulated the formation of essential intermediates by the condensation of tryptophan with dihydroxyphenylalanine and then with formaldehyde as shown in (1)–(3), to give intermediates (3) that could be transformed into the yohimbine, strychnine skeletons by suitable processes of ring fission or expansion, reduction and further changes as shown briefly in formulae (4)–(11). However Wenkert and Bringi[12, 13] pointed out that any acceptable theory of biogenesis of the indole alkaloids must satisfactorily account for the following observed facts.

(a) Ring E in the yohimbine series is only found aromatic in alstoniline (12).

(b) Apart from alstoniline (12) and sempervirine (13) all the bases of the yohimbine group have asymmetric carbon atoms at the points of fusion of rings D and E and of these C-15 always has the same absolute configuration, which is identical with that of the same carbon atom in all bases in the ajmalicine–corynantheine, and strychnine groups (except (±)-mitraphylline and (±)-akuaminicine).

(c) The bases of the yohimbine-ajmalicine–corynantheine group all contain a carbomethoxy or similar group in the same position.

To explain these facts they propose that rings D and E in this group are derived from a non-aromatic precursor and, since the natural


COOH
NH2
H2N
COOH
OH
OH
(1)
(2)
NH2
CHO
(3)
(4)
OH
OH
NH
(5)
OH
OH
HCHO
NH
(7)
HO
OH
HCHO
N
(8)
HO
OH
N
(6)
OH
OH
N
CHO
CH2OH
(10)
N
O
O
(11)
N
(9)
MeOOC
OH
N
N
MeOOC
(12)
N
N
(13)

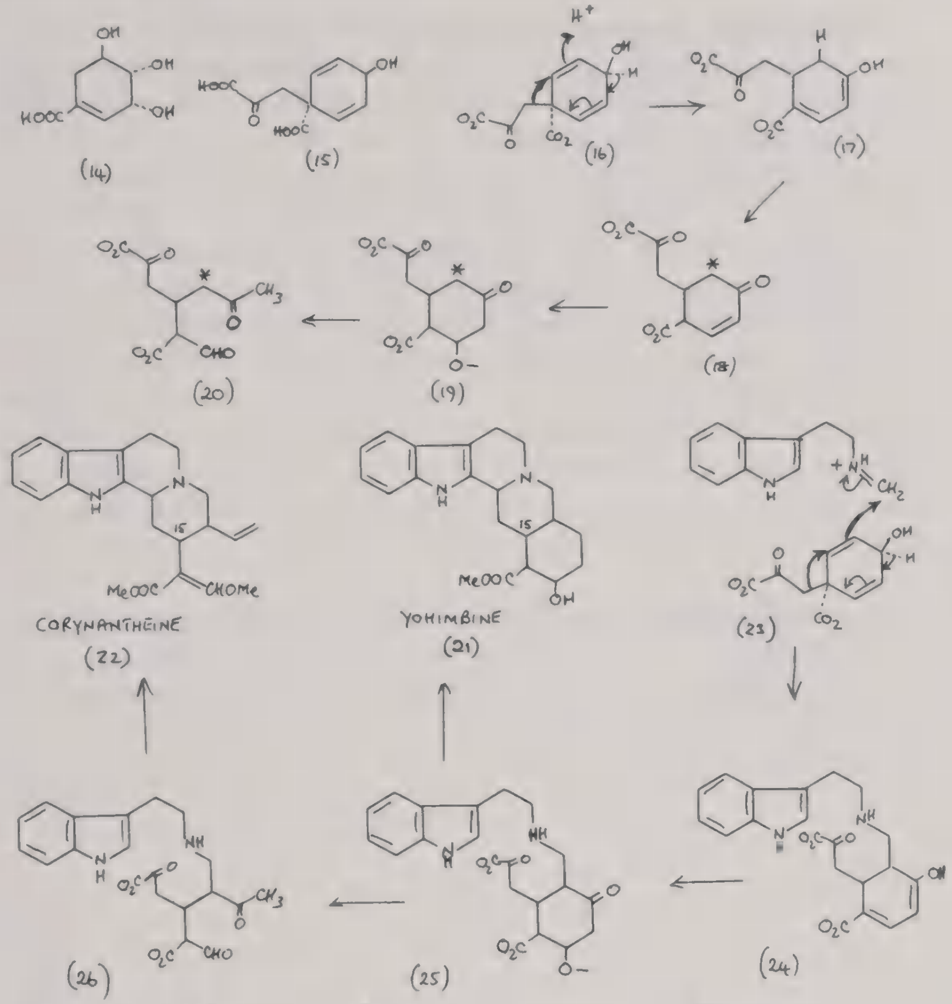
progenitors of phenylalanine have been shown to be shikimic acid (14) and prephenic acid (15), the latter is chosen as the most likely precursor of the relevant rings of the indole alkaloids.[12, 13] Prephenic acid could suffer rearrangement, hydration and retro-aldolization by the processes set out in formulae (16)→(20) to give the intermediates (19) and (20) (with active centres marked by asterisks), the structural units of which are readily discernible in yohimbine (21) and corynantheine (22).

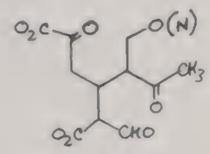
Prephenic acid is a symmetrical and hence optically inactive compound and might be expected to yield racemic products, but the intervention of an enzyme system in the steps (16) → (17) could reasonably result in a uniform absolute configuration of alkaloids at C-15. The origin of (±)-mitraphylline and (±)-akuammicine, the only two valid exceptions to the uniformity of configuration as C-15, could be explained by the non-intervention of such a system. It has recently been shown that '(±)-mitraphylline' is almost certainly the (–)-form, contaminated with isomitraphylline, which is dextrorotatory and very easily formed from (–)-mitraphylline.

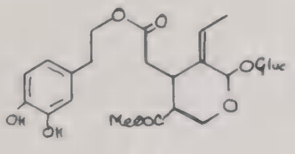
The intervention of the conjugate acid of *N*-formyltryptamine in place of H in (16) would give rise as in (23) to the intermediates (25) and (26), which require only union of the carbonyl group of the pyruvate side chain with the tryptamine nitrogen and the indole α-position followed by relatively simple changes to give yohimbine (21) and corynantheine (22) and related bases.

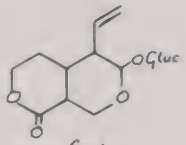
Similarly the conjugate acid of formaldehyde or formaldimine could also be involved in the rearrangement of prephenic acid leading eventually to what Wenkert has called the '*Seco*-prephenate-formaldehyde' (SPF) unit (27). This unit may be an important cell-constituent of higher plants and may give rise to a wide variety of superficially unrelated plant products. For example the natural products oleuropeine (28), gentiopicrin (29), swertiamarin (30) and bakankosin (31) appear to be derived from this type of unit.

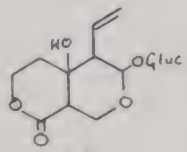
The other types of indole alkaloid can be rationally derived from the same SPF-type of precursor in the following manner.[12, 13]




(27)
'SPF' UNIT


(28)


(29)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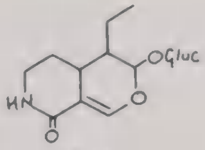
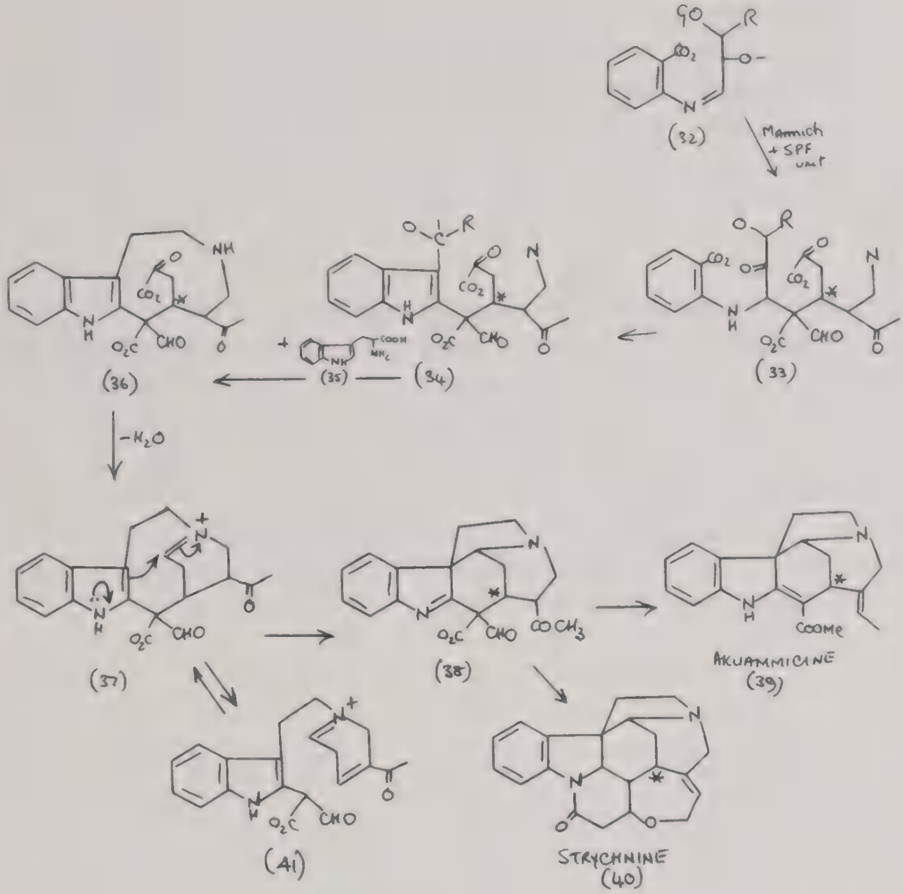
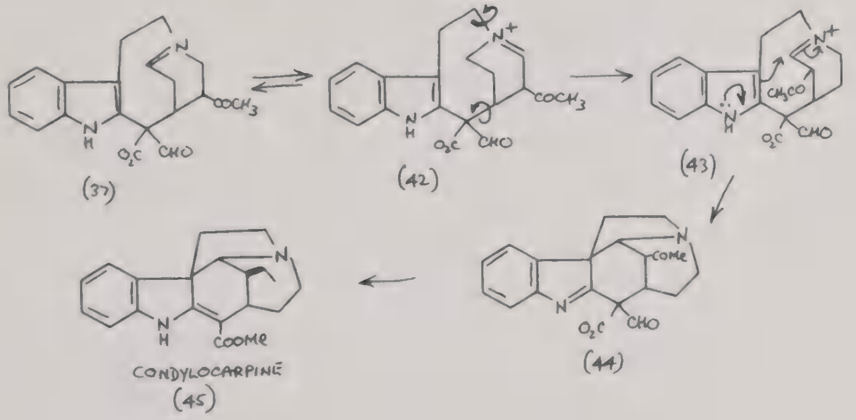

(31)

A. **Strychnine, akuammicine** Glycosylideneanthranilic acid (32) is a tryptophan progenitor. α-Oxidation of (32) followed by Mannich condensation of the product with an SPF unit could yield the intermediate (33), and this, following a metabolic pathway analogous to the formation of tryptophan, could then lead through (34) to (35); final cyclization to (36), (37) and (38) and the transformation of the last of these into akuammicine (39) and strychnine (40) then presents no obvious difficulty. The absolute configuration at the carbon atom marked with an asterisk remains undisturbed throughout, and the two bases (39) and (40) have the same arrangement at this point as the bases of the yohimbine–corynantheine group. The formation of ψ-akuammicine (racemic akuammicine) could be explained by the use of racemic intermediates or by the establishment of an equilibrium between (37) and (41) before the complete evolution of the former to the full alkaloidal skeleton.

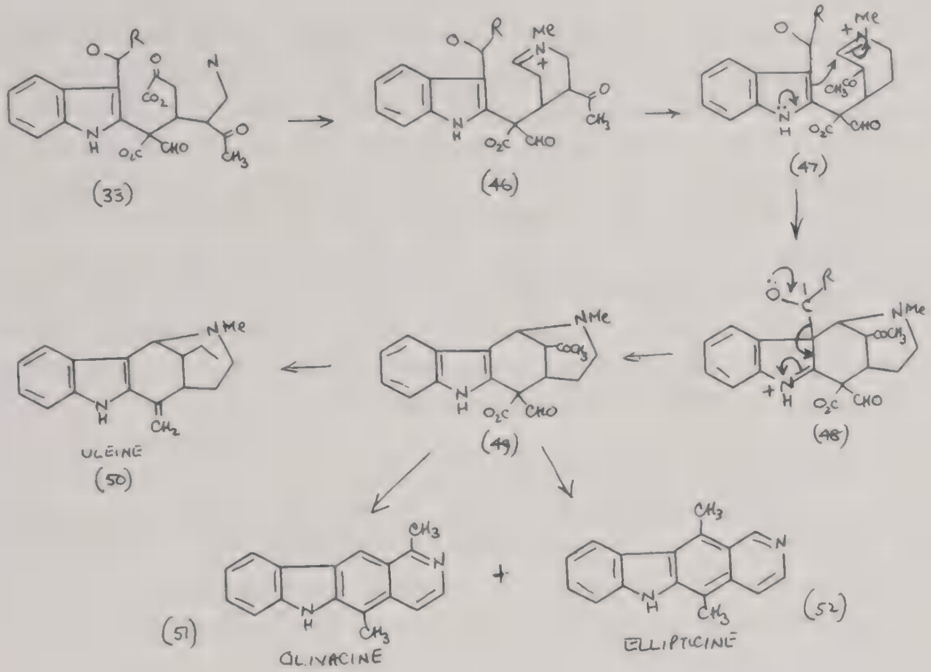
B. **Condylocarpine** Equilibration of the intermediate (37) with (42) and cyclization of this as in (43) would lead to a structural isomer of (38), namely (44), the conversion of which into condylocarpine (45) would follow a pattern similar to the conversion of (38) into akuammicine (39).

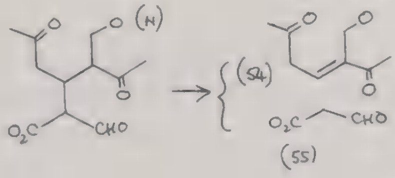

(32)
Mannich + SPF unit
(33)
(34)
(35)
(36)
$-H_2O$
(37)
(38)
AKUAMMICINE (39)
(41)
STRYCHNINE (40)

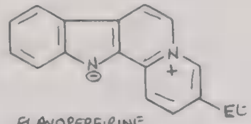

(37)
(42)
(43)
(44)
CONDYLOCARPINE (45)

C. **Uleine, olivacine, ellipticine** If the cyclization of the SPF moiety of (33) and closure with the indolic β position occurs before further progress along the tryptophan-like pathway then elimination of the β-glycosyl function by dealdolization could occur, leading through the intermediates (46), (47) and (48) to a structure (49) from which uleine (50) and, by aromatization, olivacine (51) and ellipticine (52) could arise.

D. **Aspidospermine and ibogaine** These bases, in the structures of which the SPF moiety is not immediately evident, are regarded by Wenkert as arising from a rearranged unit. A suitable rearrangement would be a retro-Michael reaction leading to fission of the SPF unit (53) into the fragment (54) and a formylacetic acid residue (55). The participation of a fragment such as (54) or the fission of such a condensation product as (26) would result in the complete loss of the formylacetic acid unit and the end product would be expected to be a base of the flavopereirine (56) type.







FLAVOPEREIRINE

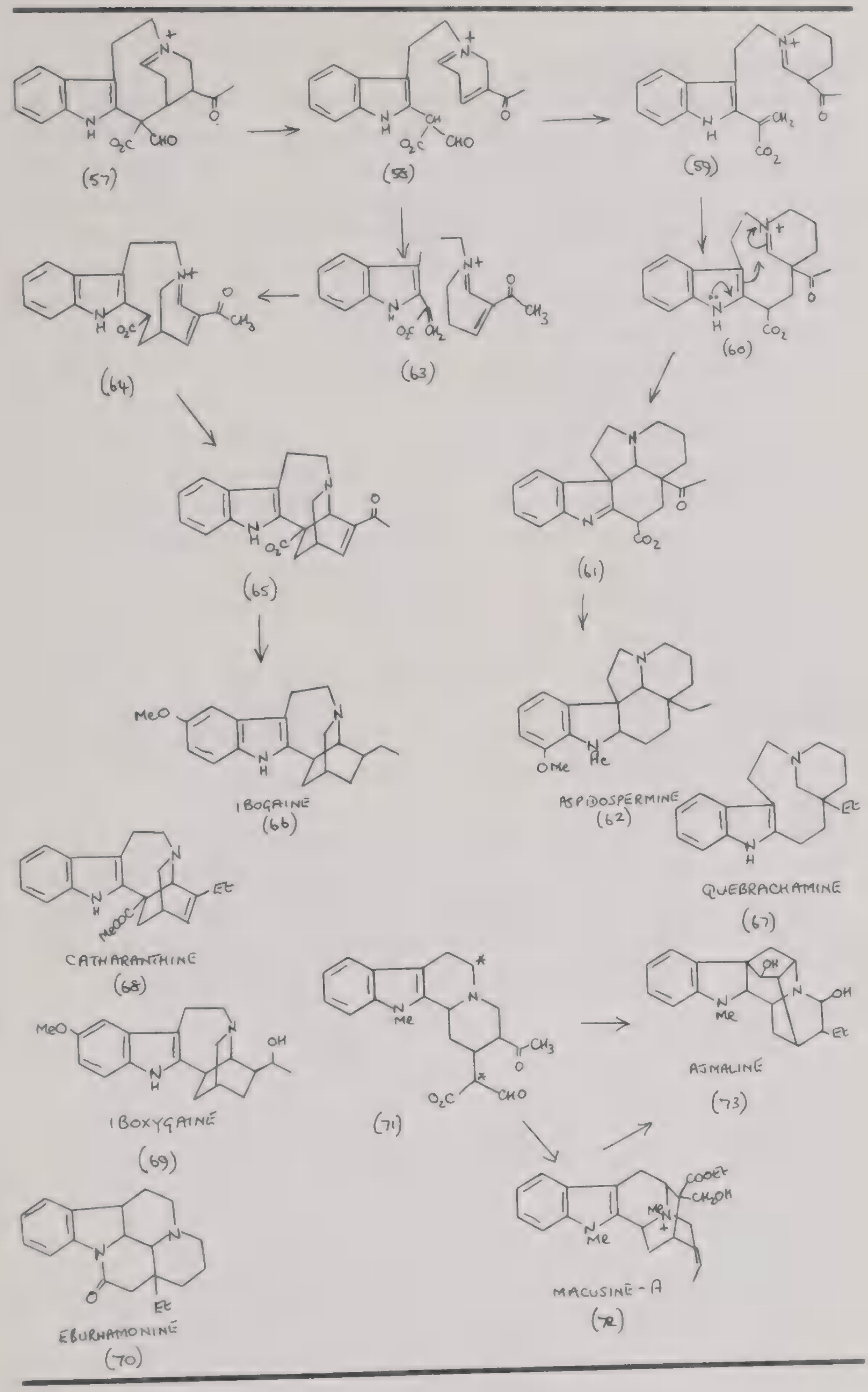
(56)

If, however, the retro-Michael reaction occurs in an intermediate such as (37) ≡ (57), the formylacetic acid residue, being attached to the indole system, is not lost, and the product (58) could then undergo a series of simple transformations as in (59)–(62) to give the aspidospermine skeleton or as in (63)–(66) to yield ibogaine. In this connection it may be noted that quebrachamine (67) corresponds to the cyclization stage (60) and both parts of the enone chromophore of (65) have been found separately in, for example, catharanthine (68) and iboxygaine (69). Further it is possibly not fortuitous that plants of the *Vinca* species elaborate bimolecular bases comprising one unit each of the aspidospermine and ibogaine types.

E. **Alkaloids of** *Hunteria eburnea.* The base eburnamonine (70) could arise from an intermediate such as (60) by closure of the new ring with the α- rather than the β-position of the indole, fission of the existing bond to the α-position and other simple changes.

It may be noted that all the *Aspidosperma* and *Hunteria* bases have a *cis*-perhydroisoquinoline system as is required by the closure of the rigid nine-membered ring in (60).

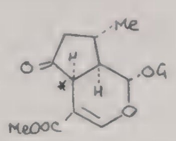
F. **Ajmaline and related bases** These are presumably derived by further cyclization of some such intermediate as (71) in the biogenesis of corynantheine; the joining of the two positions marked with asterisks in (71) could lead to a base having the structural features of macusine-A (72), and the relationship of this to ajmaline (73) is obvious.


(57)
(58)
(59)
(60)
(63)
(64)
(61)
(65)
IBOGAINE
(66)
ASPIDOSPERMINE
(62)
QUEBRACHAMINE
(67)
CATHARANTHINE
(68)
IBOXYGAINE
(69)
(71)
AJMALINE
(73)
MACUSINE - A
(72)
EBURNAMONINE
(70)

Monoterpenoid Hypothesis

In the same article in which the above ideas were advanced, Wenkert[13] has drawn attention to the fact that there are remarkable similarities between plant products such as verbenalin (74), genipin (75), aucubin (76) and asperuloside (77), which appear to be based on the monoterpene unit (78), the neutral substances oleuropeine (79), gentiopicrin (80), swertiamarin (81) and bakankosin (82) previously mentioned as derived from the SPF unit (83), and the non-indole portions of such alkaloids as corynantheine (84), yohimbine (85) and strychnine (86). For example all these have fundamental C_{10} skeletons, all have the same absolute configuration as far as is known at the asymmetric centre marked by an asterisk in formulae (74)–(86), and cleavage of the cyclopentane ring of formulae (74)–(77) at the point marked by a dotted line in (75) would make the basic skeletons of these substances identical with those of compounds derived from the SPF unit. It is possible, of course, that this similarity of structure is fortuitous, but equally the possibility that the indole alkaloids are derived essentially from acetic and mevalonic acids (or alternatively that the cyclopentane group of monoterpenes is derived from prephenic acid) cannot at this time be excluded. If indeed these alkaloids are derived from monoterpene units the yohimbine-like arrangement of ring E would follow rather than precede the corynantheine type, e.g. some such process as (87) → (88) would be involved.

Very little has been done to provide experimental support for the above very attractive theories, but it may be stated that the amide (89) readily cyclizes in hot acetic acid and sodium acetate to the amide (90),[11] the resemblance of which to akuammicine (91) is obvious. Also



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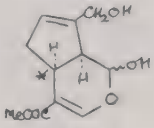

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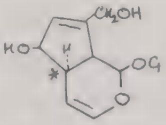

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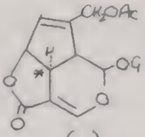

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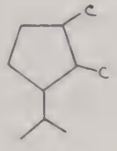

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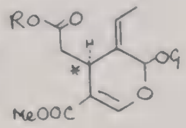

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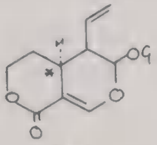

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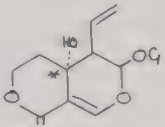

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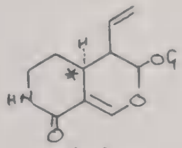

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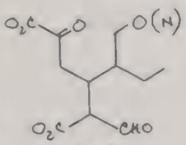

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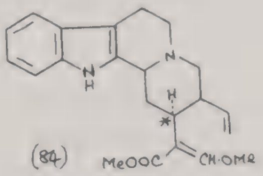

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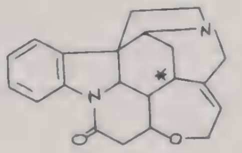

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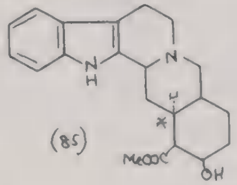

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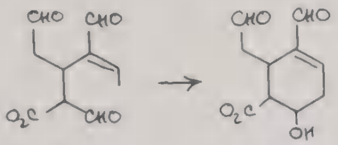
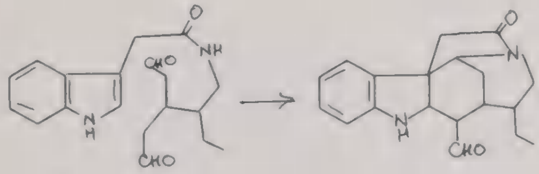
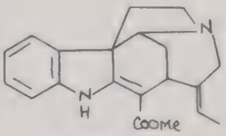


(87) (88)



(89) (90)

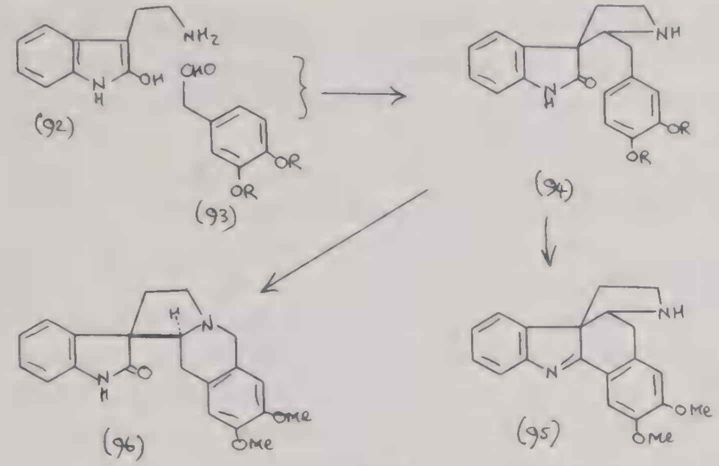


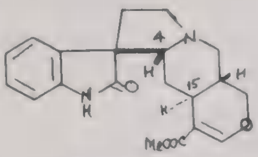
AKUAMMICINE
(91)

2-hydroxytryptamine (92) and the aldehydes (93, R = H and Me) react spontaneously at room temperature to give a good yield of the bases (94, R = H and Me) in which the stereochemistry at the two asymmetric centres is the same as that at the corresponding points in strychnine (86).[8] The base (94, R = Me) has been cyclized to (95) and condensed with formaldehyde to the base (96), the structure of which resembles that of mitraphylline (97) and its C-4 : C-15 diastereoisomer uncarine-A. On Wenkert's hypothesis this last-named alkaloid and related bases doubtless arise from 2-hydroxytryptamine or its equivalent and the SPF unit by the same sort of condensation.

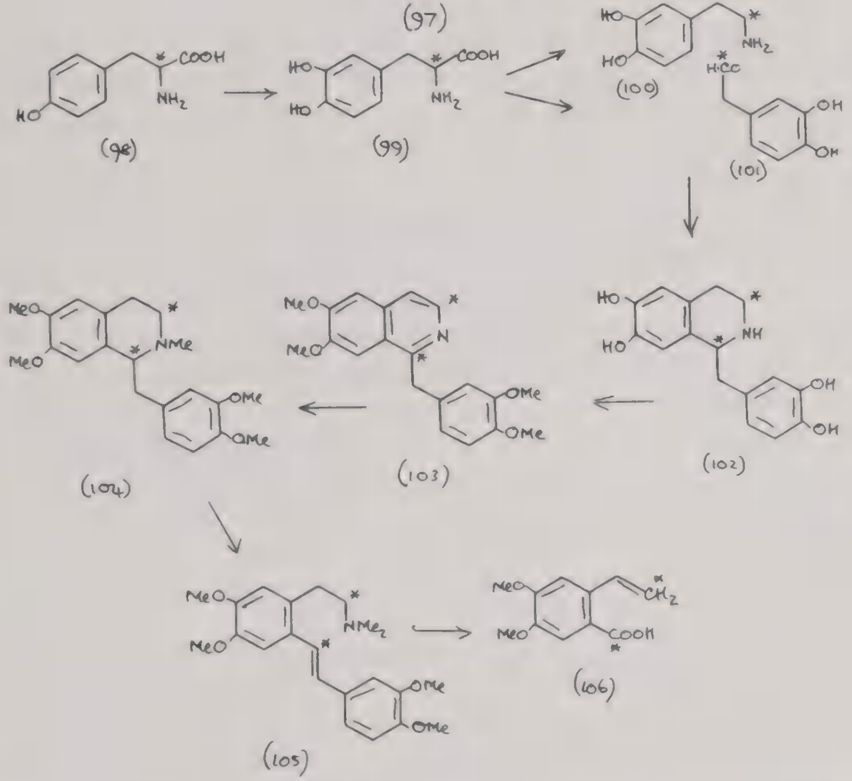
THE BENZYLISOQUINOLINE AND AMARYLLIDACEAE ALKALOIDS

Since the publication of Part I of this series considerable progress has been made in the study of the processes involved in the biogenesis of the alkaloids of the benzylisoquinoline series. By radioactive tracer work and plant feeding experiments it has been shown[4] that tyrosine is a precursor of the bases in this group. Papaverine (103), obtained from *Papaver somniferum* fed with tyrosine specifically labelled with ^{14}C as indicated by the asterisk in formula (98), was converted into (±)-laudanosine (104) and this was degraded through (105) to (106) in which all the radioactivity of the original papaverine was found, by





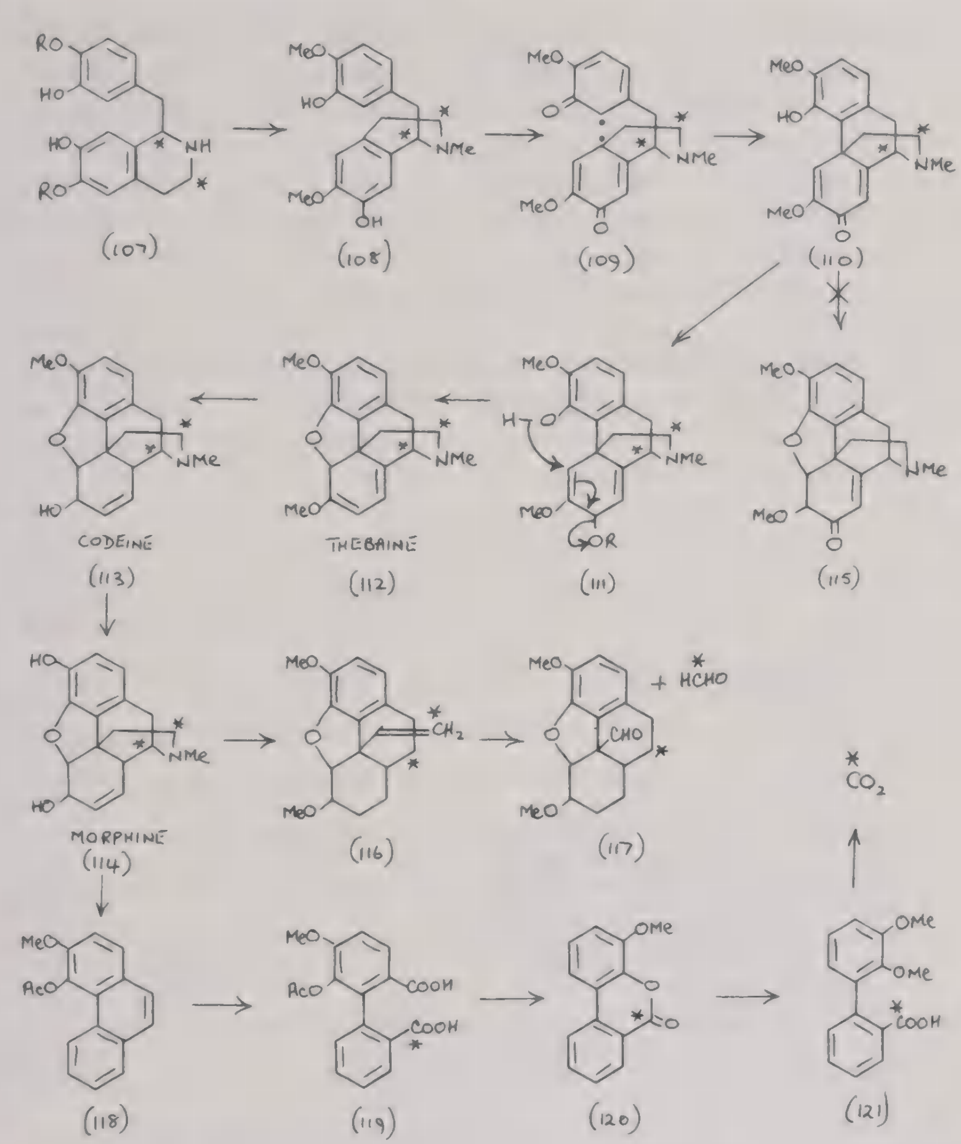
MITRAPHYLLINE
(97)



ozonolysis and decarboxylation, to be equally distributed between the two points marked with an asterisk. These results support the hypothesis of the biogenesis of papaverine by the route shown in (98) → (103).

The origin of morphine, codeine and thebaine from precursors of the benzylisoquinoline type has also been supported by the feeding of *P. somniferum* with labelled tyrosine (98) and also labelled norlaudanosoline (106, R = H) and noreticuline (107, R = Me). The last of these bases was incorporated into morphine in greatest amount, suggesting that it is a nearer approach to the actual precursor than other bases, and indeed on the basis of the oxidative hypothesis set out in formulae (107) → (114) it is the most likely immediate precursor, since in this the possibilities of other coupling reactions occurring is reduced to a minimum. The feeding experiments (and others in which poppy plants were grown in an atmosphere containing $^{14}CO_2$[10]) revealed that the first recognizable alkaloid to be formed is thebaine and that this is converted successively into codeine and morphine. The morphine obtained in this way from norlaudanosoline (107, R = H) was degraded as shown in formulae (114) → (116) → (117) and (114) → (118) → (121) → CO_2 to show that all the radioactivity was located at the points marked in (114) with an asterisk and that it was equally divided between these points.

It was suggested originally,[6, 7] that cyclization of the 4,5-oxygen bridge during the biogenesis of morphine alkaloids involved the loss of the C-7 oxygen substituent, since the only natural bases of this group having such a C-7 substituent contain no 4,5-bridge. It has recently been shown that the base (110), prepared from thebaine, does not cyclize to the ether (115) but on reduction furnishes a pair of diastereoisomeric alcohols (111, R = H) that readily give thebaine under acid conditions.[1] In the biogenesis of thebaine the group R in (111) may well be a phosphoric acid residue.


(107)
(108)
(109)
(110)
(111)
THEBAINE
(112)
CODEINE
(113)
MORPHINE
(114)
(115)
(116)
(117)
+ HCHO
CO₂
(118)
(119)
(120)
(121)

The biogenesis of the *Amaryllidaceae* alkaloids presumably follows a pattern similar to that of morphine. Suitable schemes for the synthesis of these bases are represented in formulae (122)–(134). Tyrosine (122) could be converted into a phenolic amine of type (123) in which *p*/*o*′ coupling could eventually lead to lycorine (127). A simple derivative of this type, belladine (128, R = Me), has been found in *Amaryllis belladonna* and by suitable *o*/*p*′ coupling of a demethylated base, narwedine (130) could arise, whereas *p*/*p*′ coupling (131) → (132) could eventually lead to the crinine (134) structure. In feeding experiments ^{14}C-labelled tyrosine has been incorporated into haemanthamine (135), lycorine (127) and norpluviine (136), and norbelladine (128, R = H) has been incorporated into narwedine (130), galanthamine (137), lycorine, norpluviine and haemanthamine.[2, 3, 5, 9, 14, 15]

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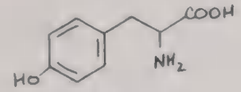

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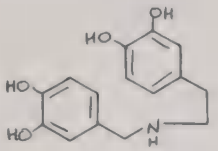

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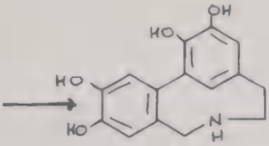

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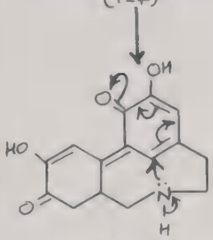

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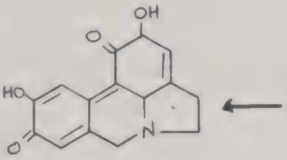

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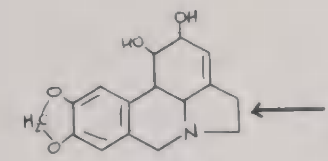
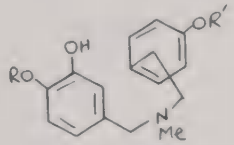
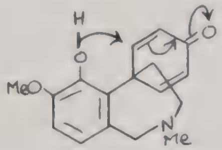


LYCORINE
(127)



(128)

R = R′ = Me = BELLADINE



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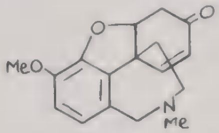
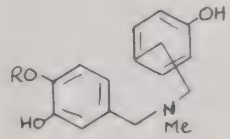


NARWEDINE
(130)



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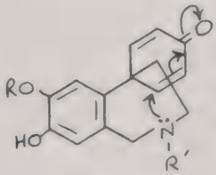

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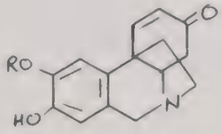

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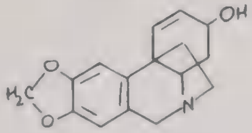

CRININE
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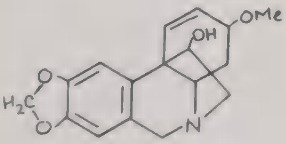

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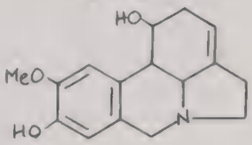

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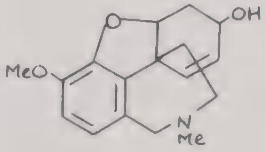

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